















Annual Report of the  
Addiction Research Center  
National Institute on Drug Abuse  
Calendar Year 1988

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Alcohol, Drug Abuse, and Mental Health Administration

5600 Fishers Lane

Rockville, MD 20857



Annual Report of the  
Addiction Research Center  
National Institute on Drug Abuse  
October 1, 1987 to December 31, 1988

Summary Statements and  
Individual Project Reports

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Alcohol, Drug Abuse, and Mental Health Administration  
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Rockville, MD 20857

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Jerome H. Jaffe, M.D., Director

Each year, the development of the Annual Report provides an occasion to survey our research program in perspective, to identify our accomplishments, assess our progress, and catalog our achievements over the past 12 months. The present report covers an additional 3 months, making the transition to our new calendar year schedule. As can be seen from the number of active projects and the publications generated, this has been a particularly busy and productive time for the Addiction Research Center. I hope that those who examine this report will agree with my own assessment that the overall quality of our program is now generally quite high, and that it is clearly excellent in our more highly developed areas of concentration.

Although the basic organization of the Center has remained stable over the past year, changes in emphasis and levels of activity have required the formation of several additional laboratories. These are described in the statements of the individual branch and laboratory chiefs. New areas of emphasis have also emerged, while others have grown in depth and dimension. The number of new projects involving cocaine is particularly noteworthy.

The programs we have mounted and the progress we have made are due, in large measure, to the unstinting efforts of a talented and dedicated scientific staff. Much credit is also due our visiting scientists, staff fellows, and other non-permanent members of our staff whose fresh ideas and enthusiasm have added vitality to our efforts. We have continued to broaden and reinforce our collegial relationships with others in the scientific community, particularly those with whom we share the campus at the Francis Scott Key Medical Center. We are glad to have had the opportunity to lend them our resources and expertise and to be the beneficiaries of their reciprocal contributions.

I would also like to mention the contribution of the members of our administrative staff and our research support staff, whose efforts have been essential to whatever we have achieved. For the quality and balance of our research program, I owe much to the continued advice and guidance of our Board of Scientific Counselors. For continued encouragement and financial support, I am grateful to the leadership of the Institute, and of the Agency.

While taking satisfaction in our accomplishments, much remains to be done and I look forward to the new opportunities ahead to advance our knowledge of drug abuse and dependence, and to improve the means of treating and preventing these disorders.



## Clinical Biology Branch

Jerome H. Jaffe, M.D., Acting Chief

### Overview

The Clinical Biology Branch conducts research in human subjects on the abuse potential of drugs; the causes, effects, treatment and prevention of addictive processes; the effects of drugs of abuse on psychological and physiological functions; and on new agents that might prove useful in treating or preventing drug dependence. These studies may involve the investigation, development and improvement of treatment agents used for drug intoxication, detoxification, and long-term rehabilitation across a number of drugs of dependence, including opioids, cocaine, anxiolytics, nicotine and marijuana. This Branch also conducts studies designed to characterize the metabolic disposition of drugs of abuse, to analyze drugs of abuse in biological fluids, and to develop model compounds for pharmacological investigations.

An area of investigation receiving increasing emphasis includes studies involving cocaine and those designed to investigate the factors which may impact the biology and psychology of vulnerability. Such studies, currently aimed at understanding the biological and psychological factors that contribute to conduct disorder in adolescents and sociopathy in adults, are multidisciplinary in nature and involve neurophysiological, neuroendocrine and psychological assessments.

In view of the common interests shared by the Biology of Vulnerability and the Psychology of Vulnerability Laboratories, as well as the fact that they function more or less as a single unit, plans have been made to merge these laboratories. Hence, the project reports for this joint group are designated BPVL. Studies in these Laboratories continue on neuroendocrine and neurotransmitter responses to differential psychological factors, e.g., aggressiveness and impulsivity. Several new projects on cocaine were added, ranging from those addressing basic mechanisms of action associated with cocaine's reinforcing properties to potential new therapeutic approaches for its abuse and dependence. Studies on the factors and co-factors that contribute to the initiation, maintenance, and cessation of self-administration of cocaine, opiates, and other drugs have also been pursued. In addition, new approaches which may be used to further examine variables which impact drug use and abuse, such as the development of a test paradigm to deliver drugs in aerosol form, are being investigated.

In addition to these areas of research, the newly designated Neuroendocrinology and Immunology Laboratory, which was a Section previously, has achieved full laboratory status. As such, this Laboratory is now responsible not only for coordinating clinical studies on the effects



of drugs of abuse on the immune system, for testing sera for HIV antibodies, and for raising monoclonal antibodies against new treatment drugs and drugs of abuse which do not hold proximate commercial value, but also for assuming a major role in the design and execution of basic studies directed toward elucidating neuroendocrine mechanisms consequent to, and/or underlying, drug use and abuse. Current emphasis of this Laboratory includes studies on the effects of drugs, including cannabinoids and inhaled nitrites, on the immune system and neuroendocrine responses to drugs, with particular emphasis on cocaine, as well as several studies investigating factors which may contribute to HIV infection.

While work continued in the Chemistry and Drug Metabolism Laboratory on the validation of commercial drug screening assays and on human studies correlating drug levels in biological fluids with behavioral and other pharmacological effects, new studies were initiated to examine the feasibility of using saliva and hair to detect drugs of abuse. Of special interest is the potential use of hair as an historical record of substance abuse.

In the Biology of Dependence and Abuse Potential Assessment Laboratory, several new initiatives, including the conduct of more sophisticated studies focusing on factors which impact cigarette and smokeless tobacco dependence, as well as investigations of the subjective and performance effects of passive smoke exposure, have begun. Other new projects include studies of a new investigational opioid antagonist, abuse liability studies involving the assessment of subjective effects as well as behavioral discriminative measures, and a study on the abuse liability of mazindol.

The progress reports for each Laboratory present the projects and findings in greater detail. The various projects and ongoing work are presented under the organizational component which played the dominant role in data acquisition or analysis.

## Laboratory of Chemistry and Drug Metabolism — Edward J. Cone, Ph.D., Chief

### Overview

The Laboratory of Chemistry and Drug Metabolism performs chemical, pharmacokinetic, metabolic and pharmacodynamic studies of drugs of abuse in human subjects.

Currently underway are:

- (1) Analytical studies comparing commercially available assays which detect drugs of abuse in urine with gas chromatographic/mass spectrometric procedures;

Several existing commercial assays to detect cocaine abuse are currently being evaluated. In addition, an effort would be made to examine the validity of current test methods employed to detect opiate use by measuring opiates and/or their metabolites in a variety of biological specimens from individuals who have been administered known amounts of the compounds. Validity assessment of screening assays which detect other classes of drugs of abuse is also underway.

- (2) Investigations examining the feasibility of using saliva samples to test for cocaine, marijuana and opiates as well as determining whether levels of these compounds in saliva will correlate with behavioral and physiological effects;

- (3) A project determining the relationship of blood, saliva and urine levels of marijuana and certain cannabinoid metabolites to behavioral effects, the release of cortisol, and changes in performance observed after acutely administered marijuana;

- (4) Studies examining the relationship of blood and saliva levels of opiates to the resulting pharmacologic effects;

These studies investigate both the pharmacokinetics and pharmacodynamics of opiates and are designed to determine the relationship of behavioral and physiological effects produced by opiates to levels of these compounds and/or their metabolites in body fluids. Moreover, efforts are being directed toward determining if a metabolic marker for heroin abuse can be found in urine.

- (5) Studies evaluating the utility of hair samples as an historical record of substance abuse.

In addition, the Laboratory performs basic research in the area of methodology development. New analytical methods are being developed to measure drugs of abuse in body fluids which may represent improvements over existing methods because active substances will be measured, in contrast to inactive metabolites.

The Laboratory has also devised a specific and sensitive assay for tetrahydrocannabinol (THC), the active constituent of marijuana. This new assay may provide a new analytical tool for studying the effects and mechanisms of action of marijuana. This type of research strategy is also being employed to develop analogous approaches for other drugs of abuse.

In summary, the Laboratory performs basic research in the area of the chemistry of substance abuse. Studies range from fundamental studies into the mechanisms of action of drugs to more practical studies assessing the validity of test methods currently employed to detect drugs in body fluids.

### **Summary of Ongoing Research**

Specific research projects which were actively pursued in the past year are briefly summarized below. Only those findings for which personnel from this Laboratory were principal investigators are reviewed.

#### **A. Validity Studies of Commercial Drug Screening Assays: Cone, E.J.; Collaborating Investigators: Mitchell, J. and Mell, L.**

The aim of this study is to examine the validity of new commercial assays which detect drugs of abuse in the urine using clinical specimens obtained from drug users. Eight commercial assays for cocaine were tested to evaluate the validity of the resulting data. A comparison was made between results obtained using these various commercial approaches and those obtained using gas chromatography/mass spectrometry. Analogous studies are also underway with screening assays commonly used for opiates. It is hoped that the use of clinical samples, rather than samples spiked with known compounds, will generate novel information about the time course of detection, as well as the specificity and accuracy, of these various assay procedures.

#### **B. Detection of Drugs of Abuse in Human Saliva: Cone, E.J.**

The goal of this study is to determine the feasibility of performing drug testing using saliva samples. Cocaine, marijuana, or opiates were administered and saliva and blood samples collected thereafter along with concurrent collection of behavioral and physiological assessments. The biofluids were analyzed using gas chromatography or radioimmunoassay. In the case of cocaine, the results demonstrated that statistically significant correlations exist between blood levels and saliva levels. Studies are ongoing for



marijuana and opiates. Findings from these studies could provide data upon which to justify the development of new non-invasive tests for drug abuse.

**C. Acute Effects of Marijuana in Humans: Cone, E.J.;**  
**Collaborating Investigator: Johnson, R.E.**

The goal of this study is to determine the relationships of blood, saliva, and urine levels of marijuana and certain cannabinoid metabolites to the behavioral effects, release of cortisol, and changes in performance associated with smoking, oral ingestion, or passive inhalation of marijuana smoke.

Preliminary results had indicated that subjects experience a marijuana high from ingesting marijuana-laced brownies, but that the onset of activity is slower and the time course more prolonged than smoking. Therefore, in this study, subjects smoked or consumed the equivalent of one or two standardized marijuana cigarettes or were passively exposed to the smoke of 4 or 16 marijuana cigarettes; physiological and behavioral effects were monitored and blood, saliva and urine samples were collected.

The results showed that, as expected, the profile of activity usually associated with acute administration of marijuana was observed. There was rapid absorption of marijuana and this was associated with a correspondingly rapid onset of behavioral effects and the release of cortisol. Further studies planned will compare the levels of tetrahydrocannabinol and its metabolites with the onset and intensity of the associated behavioral and physiological effects.

**D. Pharmacokinetics and Pharmacodynamics of Opiate Analgesics:**  
**Cone, E.J.**

The long-term goal of this project is to determine the potential value which saliva may have as a new test medium by which to detect drugs of abuse. The more immediate goal is to determine the relationship between of blood and saliva levels of single doses of opiates and the resulting pharmacologic effects. Single doses of heroin, morphine, dilaudid, codeine, oxycodone and oxymorphone are administered intramuscularly to male volunteers with a history of heroin abuse. A total of 3 test doses (i.e., placebo and two active doses) are included; pharmacological evaluation is subsequently carried out for 24 hours and biological fluids collected for 7 days. In addition, an effort is being made to determine if a metabolic marker for heroin abuse can be found in urine.

**E. Pharmacokinetics and Pharmacodynamics of Drugs of Abuse in Hair:  
Cone, E.J.**

Reports in the literature demonstrating that drug residues can be detected in human hair specimens have generated significant interest in the use of hair as an historical record of drug usage. With this as background, this study would determine the presence and time course of drugs of abuse in human hair. Healthy male subjects with a history of substance abuse would be administered drugs of abuse. Prior to and after drug administration, head and facial hair specimens, as well as blood, saliva and urine specimens, would be obtained and analyzed using radioimmunoassay and gas chromatography/mass spectrometry to determine the usefulness of hair samples as a record of substance abuse.

**Publications**

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Cone, E.J., Welch, P. and Lange, W.R.: Clonidine partially blocks the physiologic effects but not the subjective effects produced by smoking marijuana in male human subjects. Pharmacol. Biochem. Beh. 29: 649-652, 1988.

Cone, E.J., Johnson, R.E., Paul, B.D., Mell, L.D. and Mitchell, J.: Marijuana-laced brownies: Behavioral effects, physiologic effects and urinalysis in humans following ingestion. J. Anal. Toxicol. 12: 169-175, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00002-03 CDM
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Validity Studies of Commercial Drug Screening Assays		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.J. Cone	Chief CDM, ARC, NIDA
Others:	D. Darwin	Chemist CDM, ARC, NIDA
	D. Yousefnejad	Chemist CDM, ARC, NIDA
	S. Menchen	Lab Technician CDM, ARC, NIDA
	P. Welch	Nurse CDM, ARC, NIDA
COOPERATING UNITS (if any)  Naval Screening Laboratory, Norfolk, Veterans Administration (J. Mitchell and L. Mell).		
LAB/BRANCH Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.125	0.125	1.0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Commercial assays for the detection of drugs of abuse in urine change periodically and must be re-evaluated to establish the validity of the detection procedure. Hence, these studies are designed to examine the detection validity of new assays using clinical specimens obtained from drug users under controlled conditions.</p> <p>Healthy male volunteers with a history of chemical substance abuse participate in these studies. Informed consent is obtained and all procedures are approved by the hospital Institutional Review Board.</p> <p>Currently, six commercial assays for cocaine are being evaluated to determine their detection validity using specimens obtained from subjects administered cocaine. The results generated using commercial assays are being compared to those developed using gas chromatography/mass spectrometry (GC/MS) analytical procedures. Since these studies test the validity of commercial assays using clinical samples rather than "spiked" samples, they may provide unique information on the time course of detection, specificity and accuracy of these procedures in a more realistic context than tested previously.</p>		



Z01 DA00002-03 CDM

## Validity Studies of Commercial Drug Screening Assays

### Publications

Cone, E.J. and Menchen, S.L.: Lack of validity of the KDI Quik Test<sup>TM</sup> drug screen for detection of benzoylecgonine in urine. J. Anal. Toxicol. 11: 276-277, 1987.

Cone, E.J., Menchen, S.L., Paul, B.D., Mell, L.D. and Mitchell, J.: Validity testing of commercial cocaine metabolite assays: I. Assay detection times, individual excretion patterns and kinetics after cocaine administration to humans. J. Forensic Sci., In press, 1989.

Cone, E.J. and Mitchell, J.: Validity testing of commercial cocaine metabolite assays: II. Sensitivity, specificity, accuracy and confirmation by gas chromatography/mass spectrometry. J. Forensic Sci., In press, 1989.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00003-03 CDM

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Detection of Drugs of Abuse in Human Saliva

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	CDM, ARC, NIDA
	D. Yousefnejad	Chemist	CDM, ARC, NIDA
	S. Menchen	Lab Technician	CDM, ARC, NIDA
	P. Welch	Nurse	CDM, ARC, NIDA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.25

PROFESSIONAL:

0.25

OTHER:

1.0

CHECK APPROPRIATE BOX(ES).

☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To determine the feasibility of drug testing using saliva samples, the presence of drugs of abuse was studied in saliva samples obtained from human subjects after drug administration.

Healthy male subjects with a history of chemical substance abuse volunteered for the studies. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board.

Following the administration of cocaine, marijuana or opiates, saliva and blood samples were collected periodically. In addition, behavioral and physiological measures were made concurrent with the collection of biofluids. The resulting samples were analyzed using gas chromatography or radioimmunoassay.

For the cocaine samples, there were statistically significant correlations of blood levels with saliva levels. Studies are ongoing for marijuana and opiates.

The results of these studies may provide a scientific basis for the development of new non-invasive tests for drug abuse.

Z01 DA00003-03 CDM

## Detection of Drugs of Abuse in Human Saliva

### Publications

Cone, E.J. and Menchen, S.L.: Stability of cocaine in saliva. Clin. Chem., In press, 1988.

Cone, E.J., Yousefnejad, D., Darwin, D. and Menchen, S.L.: Detection of morphine and cocaine in human saliva by Coat-A-Cout<sup>R</sup> radioimmunoassay. TIAFT 88 Proceedings, In press, 1988.

Cone, E.J., Kumor, K., Thompson, L.K. and Sherer, M.: Correlation of saliva cocaine levels with plasma levels and with pharmacologic effects after intravenous cocaine administration in human subjects. J. Anal. Toxicol. 12: 200-206, 1988.

Thompson, L.K. and Cone, E.J.: Determination of delta-9-tetrahydrocannabinol in human blood and saliva by high performance liquid chromatography with amperometric detection. J. Chromatogr. 421: 91-97, 1987.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA00004-04 CDM

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Acute Effects of Marijuana in Humans

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.J. Cone Chief CDM, ARC, NIDA

Others: S. Menchen Lab Technician CDM, ARC, NIDA

P. Welch Nurse CDM, ARC, NIDA

## COOPERATING UNITS (if any)

Research Technology Branch, ARC, NIDA (R.E. Johnson)

## LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

## SECTION

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.75

## PROFESSIONAL:

0.25

## OTHER:

0.50

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To determine the relationships between blood, saliva, and urine drug levels to any resulting behavioral effects, hormone release, and human performance, the effects of marijuana were studied in male human subjects. Marijuana was administered by smoking, oral ingestion, and passive inhalation of marijuana smoke.

Healthy male volunteers with a history of marijuana use participated in the study. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Subjects smoked or consumed the equivalent of one or two standardized marijuana cigarettes (2.8% tetrahydrocannabinol [THC]), or were passively exposed to the smoke of either 4 or 16 marijuana cigarettes. In addition to samples of blood, saliva, and urine, physiologic and behavioral measures were made. Hormone and THC measures were determined for the blood samples using radioimmunoassay. Cannabinoid metabolites were measured using high performance liquid chromatography and gas chromatography/mass spectrometry. The profile of activity normally observed following acutely administered marijuana was observed; this resulted from the rapid absorption of THC and was associated with the anticipated behavioral effects as well as the release of cortisol. In contrast, the excretion of cannabinoid metabolites was prolonged. Other analyses ongoing or planned include comparing whether the biofluid levels of THC and/or its metabolites are associated with behavioral and physiologic effects.

It is hoped that these studies will further current understanding of marijuana's effects and the relationship of biofluid drug levels to changes in performance.



Z01 DA00004-04 CDM

## Acute Effects of Marijuana in Humans

### Publications

Cone, E.J., Welch, P. and Lange, W.R.: Clonidine partially blocks the physiologic effects but not the subjective effects produced by smoking marijuana in male human subjects. Pharmacol. Biochem. Beh. 29: 649-652, 1988.

Cone, E.J., Johnson, R.E., Paul, B.D., Mell, L.D. and Mitchell, J.: Marijuana-laced brownies: Behavioral effects, physiologic effects and urinalysis in humans following ingestion. J. Anal. Toxicol. 12: 169-175, 1988.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA00006-02 CDM

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pharmacokinetics and Pharmacodynamics of Opiate Analgesics

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Cone	Chief	CDM, ARC, NIDA
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Others:	D. Darwin	Chemist	CDM, ARC, NIDA
	S. Menchen	Lab Technician	CDM, ARC, NIDA
	P. Welch	Nurse	CDM, ARC, NIDA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

## SECTION

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.25

## PROFESSIONAL:

0.25

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To determine the relationship of blood and saliva levels to pharmacologic effects, the effects of single doses of intramuscularly administered opiates (i.e., heroin, morphine, dilaudid, codeine, oxycodone, and oxymorphone) are being studied in male human volunteers. Additionally, the study is being performed to determine if a metabolic marker for heroin abuse can be found in urine.

The subjects are healthy males with a history of heroin abuse. Informed consent is obtained and all procedures are approved by the hospital Institutional Review Board. A total of three test doses (placebo and two active doses) are administered in random order. Test measures are taken for 24 hours and biological fluids collected for 7 days after each test. The biological fluids will be analyzed for parent drug and metabolites using chromatographic and immunoassay techniques.

The significance of this study lies in the potential value which saliva may have as a new test medium for detecting drugs of abuse and characterizing the time course of the excretion of possible metabolic markers for heroin abuse in urine and saliva.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00007-01 CDM

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pharmacokinetics and Pharmacodynamics of Drugs of Abuse in Hair

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	P. Welch	Nurse	CDM, ARC, NIDA
	S. Menchen	Lab Technician	CDM, ARC, NIDA
	D. Darwin	Chemist	CDM, ARC, NIDA
	D. Yousefenjad	Chemist	CDM, ARC, NIDA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.75

PROFESSIONAL:

0.125

OTHER:

0.625

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Drug residues have been detected in human hair specimens by a variety of analytical techniques. These reports have generated substantial interest in using hair as a historical record of drug usage. Hence, the purpose of these studies is to determine the presence and time course of drugs of abuse in human hair.

Healthy male volunteers with a history of chemical substance abuse will participate. Informed consent will be obtained and all procedures will be approved by the hospital Institutional Review Board. Subjects will reside on the Clinical Ward of the ARC. Head and facial hair specimens will be obtained prior to, and after, administration of drugs of abuse. Blood, saliva and urine specimens will also be obtained. Analyses of tissue and biofluids for drug will be performed using radioimmunoassay and gas chromatography/mass spectrometry.

These studies may provide a scientific basis for determining the usefulness of hair as an historical record for substance abuse.



**Biology of Dependence and Abuse Potential Assessment Laboratory -- Jack E. Henningfield, Ph.D., Chief**

**Overview**

The Biology of Dependence and Abuse Potential Assessment Laboratory (BDL) is one of three laboratories in the Clinical Biology Branch of the Addiction Research Center (ARC). The purposes of this Laboratory are: first, to assess the biological basis of drug dependence using quantitative experimental procedures of the behavioral and pharmacological disciplines; and, second, to assess the abuse liability and physical dependence potential of selected compounds. These aims are intended to serve the overall mission of the ARC in providing a better foundation for both understanding and developing rational therapeutic approaches and prevention strategies for drug dependence.

The BDL evolved out of a tradition of research whose goal was to characterize drug-induced changes in behavior and physiologic function; specifically, phenomena such as drug seeking, tolerance, and physical dependence. The understanding of these phenomena and their interrelations provides much of the pharmacologic and behavioral basis for evolving theories of drug dependence. A practical product of this research was the development of standardized procedures to assess the potential of drugs to produce dependence (i.e., abuse liability and physical dependence potential tests). Early research by Himmelsbach, Frazier, Isbell, Martin, and others, produced fundamental observations upon which much of current theory about the understanding and treatment of drug dependence is based. Specific areas of exploration included the following:

- (a) the relationship between drug administration and development of tolerance, physiological dependence, and changes in mood and behavior;
- (b) the use of drug substitution and antagonist administration procedures to study the biologic basis of drug dependence and to treat addicted individuals;
- (c) the phenomena whereby drug administration could lead to the alleviation of dysphoric mood states and/or the production of euphoric mood states by the presentation of certain drugs; and,
- (d) patterns of drug-seeking in the presence and absence of pharmacologic pretreatment.

In the course of conduct of these and other basic studies, new strategies of assessment emerged. The methods included the use of observer ratings, pupilometry, cardiovascular assessment, and electroencephalogram (EEG) to provide objective markers of drug administration, as well as the development



of new instruments for assessing the effects of drugs on mood, feeling, and behavior. Data obtained using such methods and instruments proved not only to be useful in exploring the basic phenomena underlying drug dependence, but also led to objective methods of abuse liability assessment. The ability to both quantitatively and qualitatively characterize the clinical pharmacology of substances was also fundamental in development of more selective, safer, and more efficacious agents for the alleviation of human disease and suffering.

Most studies of the BDL are multidisciplinary in nature and involve collaborations with one or more other laboratories of the ARC. With such multidisciplinary efforts it is possible to quantitate the subjective, physiologic, behavioral, electrophysiologic, cognitive, pharmacodynamic, pharmacokinetic, reinforcing, aversive, and other effects of drugs, as well as to assess the biologic generality of phenomena by comparative animal-human research.

In the summary that follows, the research is divided into that which is ongoing (Section I) and that in which human testing is completed, but for which followup analyses are in progress (Section II).

#### **Special Projects During the Last Year**

**A. Surgeon General's Report: The Health Consequences of Smoking: Nicotine Addiction.** The Chief, BDL, served as a scientific editor and contributor to the Report; two Staff Fellows (R.J. Lamb, P.W. Woodson) were contributors; the Branch Secretary (P. Thomas) provided special secretarial support.

**B. Testimony to Congress.** On behalf of NIDA, the Chief, BDL, developed and presented testimony before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, July 29, 1988.

**C. National Cancer Institute Physician Training Program.** The Chief, BDL, assisted in the development of a videotaped program to train physicians to treat nicotine dependence using nicotine replacement therapy.

**D. Grant Reviews.** The Chief, BDL, served in an Initial Review Group (IRG) session and performed two center grant site visit reviews.

**E. Student Training Program.** The Chief, BDL, along with the Deputy Director, ARC, obtained funding for the third consecutive year to provide training fellowships for students.

**F. Consulting Services to the Food and Drug Administration (FDA) and the Federal Trade Commission (FTC).** The Chief, BDL, provided technical reviews and consulting advice to the Commissioner of the FDA and to the

Division of Advertising Practices of the FTC about scientific aspects of a new nicotine delivery device developed by the R.J. Reynolds Tobacco Company.

## **I. Summary of Ongoing Research**

(Note: The investigator listed first is actively directing the research under the general supervision of the Laboratory Chief; the investigators shown in parenthesis have left the ARC, but either have contributed, or continue to contribute, to the ongoing research.

### **A. Assessment of Opioid Agonists and Antagonists: Abuse Potential, Pharmacokinetics, and Pharmacodynamics: Heishman, S.J., Henningfield, J.E., Fudala, P.J., Johnson, R.E. and Cone, E.J.**

Subjects with histories of opioid abuse are studied on the Residential Research Unit to determine the possible abuse potential of nalmefene, a new investigational opioid antagonist with relatively few agonist effects. The efficacy of nalmefene in blocking the morphine's effects are also evaluated. Blood samples taken over time are analyzed to provide an assessment of the relationship between the effects of nalmefene and plasma levels of the compound and its metabolites. It is hoped that the results of this study will be useful in determining the possible utility of this long-acting opioid antagonist for the treatment of opioid-dependent persons. This study is done in collaboration with the Chemistry and Drug Metabolism Laboratory and the Research Support Branch.

Update: Preliminary subject testing has begun in the past year.

### **B. Psychotropic Properties of Stimulants and Sedatives: Discriminative Properties: Heishman, S.J., (Lamb, R.J.), Lange, W.R. and Henningfield, J.E.**

Subjects with histories of stimulant and sedative abuse are studied on the Residential Research Unit to determine their ability to discriminate between prototypic stimulants and sedatives using both traditional subjective effects measures and behavioral discrimination procedures. An opioid will also be evaluated in some tests involving subjects with histories of opioid abuse. It is hoped that this study will help to improve the accuracy of procedures for assessing abuse liability by quantitatively assessing similarities and differences among drugs based upon studies employing controlled exposure of human volunteers. This study will also generate a base of data obtained from human volunteers that may be compared to the extensive amount of data that has been collected using animal subjects.

Update: Subject testing began in the past year.



**C. Assessment of Mazindol for Abuse Liability: Klein, S.A., Henningfield, J.E., and Kuhar, M.J.**

Subjects with histories of stimulant abuse were studied on the Residential Research Unit to compare the abuse liability of mazindol (an anorectic agent with some psychomotor stimulant properties) to methylphenidate (a prototypic psychomotor stimulant with a known potential for abuse). One reason for conducting this study is to generate comparative data on the abuse liability of mazindol because the compound has been used in binding studies aimed at isolating the cocaine receptor. In addition, mazindol is a theoretically interesting drug since its mechanism of action, which involves blocking the reuptake of norepinephrine and dopamine, would suggest that the compound might be expected to exhibit some abuse liability. Despite this, one previous study and limited clinical experience suggest that actual abuse of the compound is not substantial. Thus, additional characterization of the clinical pharmacology of mazindol could be of importance in analytic efforts directed to dissecting out properties of substances which may be related to abuse potential as well as for considerations about drug development efforts. This study is conducted with the collaboration of the Neuroscience Branch.

Update: Subject testing began in the previous year.

**D. Interaction between Ethanol and Prostaglandin Synthetase Inhibitors: Klein, S.A., Henningfield, J.E., and George, F.R.**

Subjects with histories of moderate alcohol use are studied on the Residential Research Unit to assess the effects of ethanol following pretreatment with either acetaminophen or placebo. Acetaminophen is a prostaglandin synthetase inhibitor that has been shown to reduce several behavioral and physiologic effects of alcohol in animal studies. Alcohol appears to act, at least in part, by increasing prostaglandin levels. Thus, this drug interaction study makes use of the ARC's standard procedures for assessing abuse potential and performance effects to evaluate the possibility that antagonistic effects between acetaminophen and alcohol may be demonstrated in human subjects. This study is conducted in collaboration with the Preclinical Branch.

Update: Subject testing began in the past year.

**E. Passive Tobacco Smoke Exposure: Nicotine Absorption, Subjective Effects and Performance: Woodson, P.W., (Roache, J.D.) and Henningfield, J.E.**

Three subject groups are being compared in a study of the effects of exposure to ambient tobacco smoke (generated by a cigarette-smoking

machine) on standard measures of subjective and physiologic effects and performance. The groups are: nondeprived cigarette smokers, 12-hour smoke-deprived cigarette smokers, and nonsmokers. It is hoped that the use of the performance battery will provide a quantitative assay by which to determine if ambient levels of tobacco produce effects similar to those previously observed in studies in which nicotine is administered by cigarette smoking or by nicotine gum.

Update: Subject testing began in 1987 and is continuing as resources permit. Initial research demonstrated the safety and reliability of the procedures for inducing passive tobacco smoke exposure.

**F. Effects of Nicotine in Nonsmokers: Heishman, S.J., Snyder, F.R. and Henningfield, J.E.**

Nonsmokers are exposed to nicotine given in the form of polacrilex gum; preliminary testing suggests that this formulation is of low abuse liability and is safe if given according to proscribed procedures. Two important experimental questions are addressed in this study. One is a further evaluation of the effects of nicotine polacrilex in nonsmokers to determine the possible effects of nicotine on cognitive performance in the absence of pre-existing nicotine dependence. Notably, nicotine enhances performance in deprived smokers, but it remains to be determined if nicotine dependence is a precondition for this effect. The second question is of general import to understanding the development of drug dependence. That is, a model of daily repeated voluntary cumulative dosing will be used to determine the course of the possible development of tolerance to subjective, behavioral and physiologic actions of nicotine. Such data cannot be readily obtained with other drugs of abuse, and probably not with forms of nicotine known to have high abuse liability (e.g., cigarettes).

Update: An initial study indicated the safety of the procedures to be used as well as the low toxicity of the polacrilex. No reliable changes in performance were found to be induced by one or two exposures to nicotine. Preliminary subject testing on the present study has begun.

**G. Behavioral and Pharmacologic Factors in Nicotine Replacement for Tobacco Dependence: Henningfield, J.E., (Nemeth-Coslett, R.), Snyder, F.R., Pickworth, W.B. and Herning, R.I.**

A series of ongoing studies are being conducted to further characterize the pharmacology of nicotine polacrilex gum and to provide information about the practical clinical utility associated with its therapeutic use. These studies include assessing the effects of various doses of nicotine gum on performance and mood in



tobacco-deprived cigarette smokers, nondeprived smokers, and nonsmokers. Other studies have assessed factors that determine the dose of nicotine delivered via this route, e.g., chewing rate. Results from currently completed studies may have practical implications for the more efficacious use of the gum to treat tobacco dependence as well as for understanding the behavioral pharmacology of nicotine delivered via this route of administration.

Update: New findings from this series of studies were that chewing rate affected the functional dose of nicotine delivered by the gum and that consumption of acidic beverages (i.e., coffee and soft drinks) substantially reduced the absorption of nicotine from the polacrilex preparation.

**H. Opioid Self-Administration: Humans Compared to Animals: Heishman, S.J., (Lamb, R.J.), Henningfield, J.E. and Goldberg, S.R.**

Subjects with histories of opioid abuse are given the opportunity to receive an intramuscular injection of morphine on the Residential Research Unit to assess the effects of the schedule of reinforcement and drug paired stimuli on the strength and persistence of the behavior. In the seven subjects initially tested, rates and patterns of responding were similar to those obtained when animals have been tested under analogous conditions, confirming the power of the schedule of reinforcement as well as the cross-species generality of the effect. Interestingly, it appears that the drug-seeking behavior may persist at dose levels which appear to be subthreshold for discrimination by conventional self-report measures.

Update: Subject testing was completed on the first stage of this study; further testing will be done as resources permit.

**I. Effects of Commonly Used Drugs on Behavioral Performance in Normal Subjects (Army Contract-Related Study): Woodson, P.W., (Roache, J.D.) and Henningfield, J.E.**

Non-residential subjects are being tested in a study which is of basic interest to the characterization of the clinical pharmacology of commonly used drugs, as well as to partially fulfill contractual obligations to the Army. The study involves the use of performance assessment and other behavioral measures in an examination of the effects of prescription and nonprescription drugs in normal volunteer subjects in the non-residential paradigm. An additional purpose of these studies is to further development of standardized behavioral performance assessment batteries.

Update: Testing was completed on the alcohol versus chlorpheniramine study and final data analyses are being completed. A new protocol to compare a non-centrally acting antihistamine

(terfenadine) to diphenhydramine has been developed and approved, and the study has been initiated. This is the final study in the series of those conducted in collaboration with the Joint Working Group (Army Contract).

**J. Effects of Drugs on Cigarette Smoking and Responses to Nicotine: (Nemeth-Coslett, R.D.), Davis, F., Sampson, A., Henningfield, J.E. and Griffiths, R.R.**

In an ongoing series of studies conducted in collaboration with the Johns Hopkins School of Medicine, a variety of experimental preparations were used to assess the effects of drugs on the rate of cigarette smoking as well as on self-reported responses to smoking (e.g., satisfaction obtained by smoking). Recently completed studies included evaluations of the effects of marijuana, naloxone, nicotine gum and mecamylamine. Currently being collected and evaluated are data from the Residential Research Unit which have been (and are now being) as an adjunct to all residential studies. These data include information on the rate and pattern of cigarette smoking; they are collected from all subjects using an automated cigarette dispensing and recording system.

Update: Data on cigarette smoking behavior from the Research Unit continues to be collected and evaluated using the automated cigarette dispensing system.

**K. Archival Database Project: Haertzen, C.A., Chairman, Database Committee**

The main purpose of the Database Committee is to combine data from diverse studies and perform analyses on the combined data, building on the extensive screening/testing program initiated by the Director of the ARC at both the recruitment and admission levels. Database activity has been focused on assembling files of scores collected at the two time periods and linking these. This effort has made it possible to compare results from tests collected at the two time periods as well as to relate scores on the various tasks.

The Database Project has served several other laboratories of the ARC, and has enabled numerous collaborations on research problems such as the involvement of aggression and personality correlates in drug abuse as well as the identification of factors that may be related to treatment outcome. Depending upon the drug, data from about 200 Addiction Research Center Inventory (ARCI) tests have been entered into the database. Morphine data were entered initially; subsequently, data on amphetamine, pentobarbital, alcohol and other drugs have been included.

Update: The database system continues to be refined; data are being collected and disseminated to collaborating laboratories and six

manuscripts are in various stages of preparation and/or editorial review. One analysis suggests that hostility, as measured by the Jenkins Composite Hostility Scale, is a general predictor of drug-induced effects such as euphoria.

## II. Summary of Projects in Which Human Testing is Completed.

### A. Triazolam Self-Administration: Effects of Yohimbine Pretreatment: (Roache, J.D.), Klein, S.A., (Meisch, R.A.), Henningfield, J.E. and Jaffe, J.H.

Subjects with histories of sedative abuse were studied on the Residential Research Unit to determine the possible effects of an experimental model of anxiety induction (yohimbine pretreatment) on responses to a rapidly-acting benzodiazepine (triazolam). Completion of testing in 3 subjects revealed that: (1) yohimbine pretreatment did produce responses characteristic of anxiety; (2) triazolam self-administration appeared to be increased by yohimbine pretreatment; and, (3) triazolam produced deficits on performance and memory tasks to which some tolerance developed. A manuscript is in preparation.

### B. Comparative Studies of Intravenous Drug Self-Administration by Monkeys and Human Volunteers: Nicotine and Cocaine. Henningfield, J.E., (Nemeth-Coslett, R.D.), Katz, J.L., Schindler, C.W. and Goldberg, S.R.

Volunteers were given access to intravenous nicotine and delivery in a paradigm similar to that employed to study the reinforcing effects of drugs in animals. Such studies permit comparison of findings obtained with animals and humans and thereby offer the opportunity to cross-validate human and animal models of drug abuse. In addition, the studies can yield data not possible from studies conducted with either species alone. For instance, the effects of drug-associated stimuli on drug self-administration as well as on the occurrence of subjective effects can be investigated using humans, yet studies with animals permit a much more extensive range of test conditions.

In brief, the studies showed that there was a considerable degree of cross-species generality in the functional effects of variables such as dose and schedule of reinforcement. In addition, an intensive study of the effects of cocaine-paired stimuli showed that these could be of important factors involved in the maintenance of drug-seeking behavior as well as in the susceptibility to relapse. Manuscripts are in preparation.



- C. Acquisition of Dependence to Cigarettes and Smokeless Tobacco: Henningfield, J.E., Haertzen, C.A., Fagerstrom, K.O., (Nemeth-Coslett, R.D.), and Radzius, A.

A survey was conducted in collaboration with the Johns Hopkins University School of Medicine to retrospectively assess the patterns of use of cigarettes and smokeless tobacco products. The questionnaire used included a scale to evaluate level of dependence (Fagerstrom Tolerance Questionnaire or FTQ). Preliminary analyses revealed that the acquisition of tobacco use is marked by a gradual increase in use over many (8+) years in most tobacco users. Approximately 5% of cigarette smokers remained "chippers" (less than 6 cigarettes per day) for more than two years. There were no clear correlates of dependence development during early exposure to tobacco; however, smoking rates found at 6 months were related to smoking rates and levels of dependence 8 years or more later. Another analysis showed that the nicotine yields of different cigarette brands were related in a curvilinear fashion to dependence. That is, smokers of highest nicotine-yielding brands had the highest scores on the FTQ. Manuscripts are in preparation.

- D. Cholinergic Agonists and Antagonists (Army Contract-Related): (Roache, J.D.), Henningfield, J.E. and Herning, R.I.

Human volunteers without histories of drug abuse, except for cigarette smoking, were tested to assess the possible adverse performance effects of a cholinergic agonist and antagonist, given singly and in combination. The Army Performance Assessment Battery, including components of the Triservices Performance Assessment Battery (PAB), was used to evaluate behavioral performance. Manuscripts are currently in preparation.

- E. Factors Influencing Behavioral and Physiological Response to Opioids: Henningfield, J.E., (Higgins, S.T.), (Preston, K.L.), Cone, E.J. and Jaffe, J.H.

Postaddicts and nonopioid users have been reported to respond differentially to opioids. This project was designed to experimentally examine such population differences in response to mu and kappa opioids on subjective, behavioral, physiological and neuroendocrine parameters using postaddicts and opiate-naive normal residential volunteers. In the initial study (completed), the effects of single doses of naloxone following either placebo or morphine pretreatment were studied in subjects with histories of opioid dependence. Laboratory testing is complete on the first phase of the study. Initial results suggest that a single dose of morphine produces a sufficient level of physical dependence that a mild morphine withdrawal-like effect was observed when the opioid antagonist, naloxone, was subsequently administered. A manuscript is currently in preparation.

**F. Abuse Liability of Smokeless Tobacco Products: Henningfield, J.E., Radzius, A., (Nemeth-Coslett, R.D.) and Cone, E.J.**

Two smokeless nicotine delivery systems were evaluated using standardized procedures to assess the pharmacodynamic variables relevant to their potential liability for abuse, as well as the degree to which the effects produced were similar to those known to be produced by cigarette smoking. One of the systems was a commercially available smokeless tobacco product (snuff pouches) which was held in the mouth to provide buccal nicotine absorption; the other was a smokeless "cigarette" through which air was sucked to inhale vaporized nicotine. Both products produced orderly dose-related effects which were generally similar to nicotine delivered by cigarette smoke. A third smokeless nicotine delivery system, a pleasantly flavored nicotine delivering chewing gum, is currently under review for possible clinical testing. Manuscripts from the first two studies are in preparation.

**G. Physiologic Dependence to Tobacco: Cigarette Withdrawal and Nicotine Substitution: Henningfield, J.E., (Nemeth-Coslett, R.D.), Snyder, F.R., Pickworth, W.B., Herning, R.I. and Cone, E.J.**

Two intensive multidisciplinary collaborative studies were conducted using variations on the "direct addiction" and "substitution" strategies for assessing withdrawal reactions and cross tolerance. In the first study, cigarette smokers were abruptly withdrawn from tobacco for ten days, and then allowed to resume smoking. In the second study, smokers were tested in repeating cycles of 4 days smoking and 3 days abstinence; during abstinence, they were given either 0, 2 or 4 mg nicotine-containing pieces of gum to chew. A characteristic tobacco withdrawal syndrome was obtained in the first study and on 0 mg gum days in the second study. Of particular interest were certain performance and electrophysiologic data that showed little tendency to recover over the 10-day period of observation. Nicotine gum produced a dose-related blockade of withdrawal responses. Two manuscripts have been submitted for publication and four others are in preparation.

**H. Behavioral Performance and Physiologic Effects of Drugs: Atropine and Diazepam (Army Contract-Related): (Higgins, S.T.), (Lamb, R.J.), Pickworth, W.B., Herning, R.I. and Henningfield, J.E.**

Volunteers without histories of drug abuse, except cigarette smoking, were studied on the Residential Research Unit to assess the effects of atropine or diazepam on mood and performance. These studies were conducted in collaboration with the Joint Triservices Working Group. Both atropine and diazepam produced dose-related impairments on some performance measures. The differential sensitivity of the various PAB components provided useful practical



information for subsequent performance testing at the ARC and elsewhere. One manuscript is in press; four others are in preparation.

#### Papers Published or Accepted for Publication

Glover, E.D., Schroeder, K.L., Henningfield, J.E., Winn, D.M., Severson, H.H. and Christen, A.G.: A compendium of smokeless tobacco research. J. Drug Educ., In press.

Goldberg, S.R. and Henningfield, J.E. (Eds.). Meeting report: Nine papers on progress in understanding the relationship between the pharmacological effects of nicotine and human tobacco dependence. Pharmacol. Biochem. Behav. 30: 215-294, 1988.

Henningfield, J.E.: Redefining craving. NIDA Notes 2: 9, 1987.

Henningfield, J.E.: Reducing urges to smoke. Chest 92: 963, 1988.

Henningfield, J.E.: Tobacco-caused diseases are side effects of nicotine dependence. J. Med. Soc. N.J. 85(2): 108-112, 1988.

Henningfield, J.E. and Brown, B.S.: Do replacement therapies treat craving? NIDA Notes 2: 8-9, 1987.

Henningfield, J.E. and Goldberg, S.R.: Introduction: Progress in understanding the relationship between the pharmacological effects of nicotine and human tobacco dependence. Pharmacol. Biochem. Behav. 30: 217-220, 1988.

Henningfield, J.E. and Goldberg, S.R.: Pharmacological determinants of tobacco self-administration by humans. Pharmacol. Biochem. Behav. 30: 221-226, 1988.

Goldberg, S.R. and Henningfield, J.E.: Reinforcing effect of nicotine in humans and experimental animals responding under intermittent schedules of i.v. drug injection. Pharmacol. Biochem. Behav. 30: 227-234, 1988.

Henningfield, J.E., Goldberg, S.R. and Jasinski, D.R.: Abuse Liability and Dependence Potential of Nicotine. In Martin, W.R., Van Loon, G.R., Iwamoto, E.T. and Davis, D.L. (Eds.): Tobacco Smoke and Nicotine: A Neurobiologic Approach. New York, NY, Plenum Press, 1987, pp. 81-99.

Henningfield, J.E. and Jasinski, D.R.: Pharmacological Basis for Nicotine Replacement. In Pomerleau, O.F., Pomerleau, C.S., Fagerstrom, K.O., Henningfield, J.E. and Hughes, J.R. (Eds.): Nicotine Replacement: A Critical Evaluation. New York, NY, Alan R. Liss, 1988, pp. 35-61.

## Publications (Cont'd)

Henningfield, J.E., Johnson, R.E. and Jasinski, D.R.: Clinical Procedures for the Assessment of Abuse Potential. In Bozarth, M.A. (Ed.): Methods of Assessing the Reinforcing Properties of Abused Drugs, New York, NY, Springer-Verlag, 1987, pp. 573-590.

Higgins, S.T., Preston, K.L., Cone, E.J., Henningfield, J.E. and Jaffe, J.H.: Behavioral, Physiological, and Hormonal Effects of a Naloxone Challenge following Acute Morphine Pretreatment in Humans. In Harris, L.S. (Ed.): NIDA Research Monograph. Washington, DC, U.S. Government Printing Office, 1988, pp. 266-273.

Jarvik, M.E. and Henningfield, J.E.: Pharmacologic treatment of tobacco dependence. Pharmacol. Biochem. Behav. 30: 279-294, 1988.

Jasinski, D.R. and Henningfield, J.E.: Conceptual Basis of Replacement Therapies for Chemical Dependence. In Pomerleau, O.F., Pomerleau, C.S., Fagerstrom, K.O., Henningfield, J.E. and Hughes, J.R. (Eds.): Nicotine Replacement: A Critical Evaluation. New York, NY, Alan R. Liss, 1988, pp. 13-34.

Nemeth-Coslett, R.D., Henningfield, J.E., O'Keefe, M.K. and Griffiths, R.R.: Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology 92: 424-430, 1987.

Nemeth-Coslett, R.D., Robinson, N., Benowitz, N. and Henningfield, J.E.: Nicotine gum: chew rate, subjective effects and plasma nicotine. Pharmacol. Biochem. Behav. 29: 747-751, 1988.

Pomerleau, O.F., Pomerleau, C.S., Fagerstrom, K.O., Henningfield, J.E. and Hughes, J.R. (Eds.): Nicotine Replacement: A Critical Evaluation. New York, NY, Alan R. Liss, 1988.

Henningfield, J.E. and Nemeth-Coslett, R.D.: Nicotine dependence: Interface between tobacco and tobacco-related disease. Chest 90: 37S-55S, 1988.

Waranch, H.R., Henningfield, J.E. and Edmunds, M.: Letter to the Editor: Elimination of nicotine gum use following successful replacement therapy for cigarette smoking. Lancet January 2-9: 49-50, 1988.

Pickworth, W.B., Herning, R.I. and Henningfield, J.E.: Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. Pharmacol. Biochem. Behav. 30: 149-153, 1988.

Henningfield, J.E.: Improving the diagnosis and treatment of nicotine dependence (Editorial). JAMA 260(11): 1613-1614, 1988.

#### Publications (Cont'd)

Higgins, S.T., Woodward, B.M. and Henningfield, J.E.: Effects of atropine on the repeated acquisition and performance of response sequences in humans. J. Exptl. Anal. Behav., In press.

Snyder, F.R. and Henningfield, J.E.: Effects of acute nicotine deprivation and administration: Assessment on computerized performance tasks. Psychopharmacology, In press.

Rose, J.E., Sampson, A., Levin, E.D. and Henningfield, J.E.: Mecamylamine increases nicotine preference and attenuates nicotine discrimination. Pharmacol. Biochem. Behav., In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00004-04 BDL
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Comparative Self-Administration (Monkeys and Humans): Nicotine and Cocaine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R.D. Nemeth-Costlet	Staff Fellow	BDL, ARC, NIDA
	R.L. Lamb	Staff Fellow	BDL, ARC, NIDA
	S.R. Goldberg	Chief	BPL, ARC, NIDA
	C.W. Schindler	Staff Fellow	BPL, ARC, NIDA
	W.R. Lange	Medical Officer	RSB, ARC, NIDA

COOPERATING UNITS (if any)  
Behavioral Pharmacology Laboratory  
Research Support Branch

LAB/BRANCH  
Clinical Biology Branch

SECTION  
Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.12	PROFESSIONAL: 0.07	OTHER: 0.05
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CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This was a collaborative project with the BPL in which the human research was conducted on the Residential Research Unit and parallel animal studies were conducted in the BPL. The use of the self-administration (SA) study paradigm permitted an assessment of the relative contribution of environmental and pharmacologic factors to the self-administration of drugs. Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine and nicotine under similar behavioral schedules and experimental conditions also provide a means by which to assess the generality of biological variables influencing drug SA. This research has shown that responding is maintained in human subjects in the same manner in which it is maintained in non-human subjects. The stimuli that are associated with injections of cocaine develop conditioned reinforcing effects in humans in a manner similar to the manner in which these effects develop in squirrel monkeys. These studies have also demonstrated that a research strategy employing drug SA in human subjects can yield all of the important information of single-dose studies, and also can provide information on the direct reinforcing effects of a compound which may be compared to the large database on animal drug SA. These data need only to undergo final analyses before publication.

Z01 DA00004-04 BDL (Cont'd)

Comparative Studies of Drug Self-Administration in Monkeys and Human Volunteers: Nicotine and Cocaine

#### Publications

Goldberg, S.R. and Henningfield, J.E.: Reinforcing effect of nicotine in humans and experimental animals responding under intermittent schedules of i.v. drug injection. Pharmacol. Biochem. Behav. 30: 227-234, 1988.

Henningfield, J.E., Nemeth-Coslett, R.D., Katz, J.L. and Goldberg, S.R.: Intravenous cocaine self-administration by human volunteers: Second-order schedules of reinforcement. In Harris, L.S. (Ed.): NIDA Research Monograph 76. Washington, DC, U.S. Government Printing Office, 1987, pp. 266-273.

Henningfield, J.E. and Goldberg, S.R.: Pharmacological determinants of tobacco self-administration by humans. Pharmacol. Biochem. Behav. 30: 221-226, 1988.



DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00005-04 BDL
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Abuse Liability of Smokeless Tobacco Products
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)			
PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R.D. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA
	A. Radzius	Research Assistant	BDL, ARC, NIDA
	E.J. Cone	Chief	CDM, ARC, NIDA
	N.L. Benowitz	Collaborator	BDL, ARC, NIDA

COOPERATING UNITS (if any) Chemistry and Drug Metabolism Laboratory; Division of Clinical Pharmacology and Experimental Therapeutics; University of California at San Francisco;
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LAB/BRANCH Clinical Biology Branch
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SECTION Biology of Dependence and Abuse Potential Assessment Laboratory
--

INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
--

TOTAL MAN-YEARS: 0.37	PROFESSIONAL: 0.07	OTHER: 0.30
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CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>In two studies, tobacco users were tested with a commercially available smokeless tobacco product (i.e., pouches of snuff) and with a smokeless cigarette through which air is sucked to inhale vaporized nicotine. Standardized methods of abuse liability assessment were used.</p> <p>The smokeless tobacco study consisted of two phases. The first evaluated the effects of dose and the possibility that the rate of expectoration would alter nicotine extraction and effects. Dose-related changes were found in the magnitude and duration of action of measures such as reduction in the urge to smoke and the strength of the effects observed. The second phase evaluated the relationship of the effects observed to plasma levels of nicotine; these were found to be closely related to the dose administered, thus confirming the reliability of this system of nicotine delivery. The study with smokeless cigarettes indicated similar dose-related effects as those found with the commercial tobacco products; nicotine levels were negligible, suggesting the possibility that this route of nicotine administration may produce effects mediated by its peripheral stimulus properties which resemble those of smoking cigarettes.</p>
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**Abuse Liability of Smokeless Tobacco Products**

A third nicotine delivery system, a pleasantly flavored nicotine chewing gum, is currently under review for possible clinical testing of its abuse liability as well as to compare its kinetics to those of other forms of nicotine delivery systems.

**Publications**

Henningfield, J.E.: How Tobacco Produces Drug Dependence. In Ockene, J.K. (Ed.): The Proceedings of the World Congress on the Pharmacologic Treatment of Tobacco Dependence. Cambridge, MA, Institute for the Study of Smoking Behavior and Policy, 1986, pp. 19-31.

Cullen, J.W., Blot, W., Henningfield, J.E., Boyd, G., Mecklenberg, R. and Massey, M.M.: Health consequences of using smokeless tobacco (Summary of the Advisory Committee's Report to the Surgeon General). Public Health Reports 100: 355-373, 1986.

Connolly, G.N., Winn, D.M., Hecht, S.S., Henningfield, J.E., Walker, B. and Hoffman, D.: The re-emergence of smokeless tobacco. N. Eng. J. Med. 314: 1020-1027, 1986.

Glover, E.D., Schroeder, K.L., Henningfield, J.E., Winn, D.M., Severson, H.H. and Christen, A.G.: A compendium of smokeless tobacco research. J. Drug Educ., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00006-03 BDL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Triazolam Self-Administration: Effects of Yohimbine Pretreatment

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	J.D. Roache	Staff Fellow	BDL, ARC, NIDA
	R.A. Meisch	Visiting Scientist	BDL, ARC, NIDA
	S.A. Klein	Staff Fellow	BDL, ARC, NIDA
	J.H. Jaffe	Chief	BVL, ARC, NIDA
	W.R. Lange	Medical Officer	RSB, ARC, NIDA

COOPERATING UNITS (if any)

Biology of Vulnerability Laboratory  
Research Support Branch

LAB/BRANCH

Clinical Biology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.70

PROFESSIONAL:

2.00

OTHER:

5.00

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this study is to examine the effects of yohimbine pretreatment on the self-administration of triazolam in subjects with histories of sedative abuse. Two issues of relevance to the behavioral pharmacology of drug abuse are being addressed: the first involves the development of procedures to measure sedative/anxiolytic drug self-administration; and, the second is to examine the effects of yohimbine pretreatment on triazolam self-administration. It is of basic theoretical, as well as clinical, interest to define methods to detect the effects of one drug on the self-administration of another drug. In addition, yohimbine has been shown to produce neuroendocrine changes and subjective mood states in humans which resemble anxiety. Thus, this study could provide important information related to hypotheses of drug abuse which involve psychiatric vulnerability factors.

Subjects were given the opportunity to take triazolam or a placebo following pretreatment with yohimbine or placebo. Initial findings were: (1) Yohimbine pretreatment did produce responses characteristic of anxiety; (2) Triazolam self-administration appeared to be increased by yohimbine pretreatment; and, (3) Triazolam produced deficits on performance and memory tasks which appeared to show tolerance.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00007-04 BDL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Commonly Used Drugs: Effects on Behavioral Performance in Normal Subjects

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	P.W. Woodson	Staff Fellow	BDL, ARC, NIDA
	J.D. Roache	Staff Fellow	BDL, ARC, NIDA
	R.A. Meisch	Visiting Scientist	BDL, ARC, NIDA
	W.R. Lange	Medical Officer	RSB, ARC, NIDA

COOPERATING UNITS (if any)

Research Support Branch;  
U. of Minnesota (R.A. Meisch)

LAB/BRANCH

Clinical Biology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.45

PROFESSIONAL:

0.45

OTHER:

1.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The possible adverse effects of an antihistamine and alcohol on performance are being evaluated in non-residential subjects without histories of drug abuse other than cigarette smoking. The study involves the use of strategies recommended by the Joint Triservices Working Group (Army Contract) to assess behavioral (i.e., cognitive) performance. Measures include the standard Army Performance Assessment Battery (PAB), prototypic portions of the Unified Triservices Battery (UTS PAB), critical flicker fusion, and mood, as well as cardiovascular and other basic physiologic variables.

Preliminary analysis of data from the first study suggests that alcohol and chlorpheniramine produced dose-related effects on several self-report measures and mixed effects on performance across measures. These initial results suggest that the PAB is less sensitive compared to the Digit Symbol Substitution Task with respect to the level of performance disrupted by alcohol or chlorpheniramine.

A new protocol to compare a non-centrally acting antihistamine (terfenadine) to a centrally acting one (diphenhydramine) as well as to the benzodiazepine, triazolam, has been developed and approved and the study has been initiated. This is the final study in a series of those conducted in collaboration with the Joint Triservices Working Group (Army Contract).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00009-05 BDL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effects of Drugs on Cigarette Smoking and Responses to Nicotine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA
	F.C. Davis	Nurse	BDL, ARC, NIDA
	A.H. Sampson	Nurse	BDL, ARC, NIDA
	R.R. Griffiths	Collaborator	JHMU
	J.E. Rose	Collaborator	U. of California

COOPERATING UNITS (if any)

JHMU; U. of California;

LAB/BRANCH

Clinical Biology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.23

PROFESSIONAL:

0.03

OTHER:

0.20\*

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Some of these studies were conducted in the physical facilities of the Behavioral Pharmacology Research Unit at the Johns Hopkins University Medical School (JHMU) which provides some research assistant support. For example, multiple measures of cigarette smoking, subjective effects, and physiologic effects were collected during ad libitum smoking sessions in normal volunteers following administration of mecamylamine, naloxone, or marijuana. Mecamylamine had effects opposite to those observed with nicotine on several measures of smoking and subjective response: mecamylamine increased smoking and had some sedating effects. Despite this, both drugs decreased the satisfaction derived from smoking. These findings are not consistent with either the hypothesis that smoking is substantially mediated by endorphin release or the hypothesis that smoking is simply related to the level of positive subjective state.

Presently, basic measures of cigarette smoking are being collected from all subjects on the Clinical Research Unit and data analyses have begun. This database-type of study appears to be providing the opportunity to quantitate the effects of a wide range of variables on cigarette smoking (i.e., atropine administration, cocaine withdrawal, buprenorphine administration, and passive tobacco smoke exposure.



Z01 DA00009-05 BDL

## Effects of Drugs on Cigarette Smoking and Response to Nicotine

### Publications

Nemeth-Coslett, R.D. and Griffiths, R.R.: Naloxone does not affect cigarette smoking. Psychopharmacology 88: 420-425, 1986.

Nemeth-Coslett, R.D., Henningfield, J.E., O'Keefe, M.K. and Griffiths, R.R.: Effects of mecamylamine on human cigarette smoking and subjective ratings. Psychopharmacology 88: 425-430, 1986.

Nemeth-Coslett, R.D., Henningfield, J.E., O'Keefe, M.K. and Griffiths, R.R.: Effects of marijuana on human cigarette smoking and physiologic changes and subjective responses. Pharmacol. Biochem. Behav. 25: 659-665, 1986.

Nemeth-Coslett, R.D., Henningfield, J.E., O'Keefe, M.K. and Griffiths, R.R.: Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology 92: 424-430, 1987.

Rose, J.E., Sampson, A., Levin, E.D. and Henningfield, J.E.: Mecamylamine increases nicotine preference and attenuates nicotine discrimination. Pharmacol. Biochem. Behav., In press.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA00010-05 BDL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Factors in Nicotine Replacement for Tobacco Dependence

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA
	P.W. Woodson	Staff Fellow	BDL, ARC, NIDA
	R.I. Herning	Chief	CHP, ARC, NIDA
	W.B. Pickworth	Pharmacologist	CHP, ARC, NIDA
	F.R. Snyder	Statistician	CHP, ARC, NIDA
	W.R. Lange	Medical Officer	RSB, ARC, NIDA

## COOPERATING UNITS (if any)

Cognitive Studies and Human Performance Laboratory  
Research Support Branch

## LAB/BRANCH

Clinical Biology Branch

## SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.50

## PROFESSIONAL:

0.15

## OTHER:

0.35

## CHECK APPROPRIATE BOX(ES) -

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Nicotine polacrilex (chewing gum) has been under investigation as a replacement for tobacco-delivered nicotine and also as a convenient drug administration modality which provides a model of more general interest for drug dependence researchers. For example, nicotine gum was employed in initial studies to examine the capabilities of this Laboratory's recently established performance and electrophysiologic assessment approaches for evaluating drug effects. The course of research conducted using this preparation has been determined by the priorities of the ARC and the Chief of the Biology of Dependence Laboratory. These studies have included the following: (1) Effects of nicotine gum replacement on cigarette smoking and tobacco smoke exposure; (2) Pharmacodynamic effects of nicotine gum compared to other routes of nicotine administration; (3) Abuse liability of nicotine gum; (4) Dose-related effects on subjective, behavioral, and physiologic variables, including studies of the factors which may affect the functional dose, such as chewing and swallowing rates; and, (5) Effects of nicotine gum administration on learning and performance in non-smokers.

Behavioral and Pharmacologic Factors in Nicotine Replacement for Tobacco Dependence

Publications

Nemeth-Coslett, R.D., Benowitz, N.L., Robinson, N. and Henningfield, J.E.: Nicotine gum: Chew rate, subjective effects and plasma nicotine. Pharmacol. Biochem. Behav. 29: 747-751, 1988.

Pickworth, W.B., Herning, R.I. and Henningfield, J.E.: Electroencephalographic effects of nicotine gum in humans. Pharmacol. Biochem. Behav. 25: 879-882, 1986.

Jasinski, D.R. and Henningfield, J.E.: Conceptual Basis of Replacement Therapies for Chemical Dependence. In Pomerleau, O.F., Pomerleau, C.S., Fagerstrom, K.O., Henningfield, J.E. and Hughes, J.R. (Eds.): Nicotine Replacement: A Critical Evaluation. New York, NY, Alan R. Liss, 1988, pp. 13-34.

Waranch, H.R., Henningfield, J.E. and Edmunds, M.: Letter to the Editor: Elimination of nicotine gum use following successful replacement therapy for cigarette smoking. Lancet January 2-9: 49-50, 1988.

Snyder, F.R. and Henningfield, J.E.: Effects of acute nicotine deprivation and administration: Assessment on computerized performance tasks. Psychopharmacology, In press.

Pickworth, W.B., Herning, R.I. and Henningfield, J.E.: Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. Pharmacol. Biochem. Behav. 30: 149-153, 1988.

Pomerleau, O.F., Pomerleau, C.S., Fagerstrom, K.O., Henningfield, J.E. and Hughes, J.R. (Eds.): Nicotine Replacement: A Critical Evaluation. New York, NY, Alan R. Liss, 1988.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00012-05 BDL												
PERIOD COVERED October 1, 1987 to December 31, 1988														
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Factors Influencing Behavioral and Physiologic Response to Opioids (Mu Project)														
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 35%;">PI: J.E. Henningfield</td> <td style="width: 35%;">Chief</td> <td style="width: 30%;">BDL, ARC, NIDA</td> </tr> <tr> <td>Others: S.T. Higgins</td> <td>Staff Fellow</td> <td>BDL, ARC, NIDA</td> </tr> <tr> <td>E.J. Cone</td> <td>Chief</td> <td>CDM, ARC, NIDA</td> </tr> <tr> <td>J.H. Jaffe</td> <td>Director</td> <td>EVL, ARC, NIDA</td> </tr> </table>			PI: J.E. Henningfield	Chief	BDL, ARC, NIDA	Others: S.T. Higgins	Staff Fellow	BDL, ARC, NIDA	E.J. Cone	Chief	CDM, ARC, NIDA	J.H. Jaffe	Director	EVL, ARC, NIDA
PI: J.E. Henningfield	Chief	BDL, ARC, NIDA												
Others: S.T. Higgins	Staff Fellow	BDL, ARC, NIDA												
E.J. Cone	Chief	CDM, ARC, NIDA												
J.H. Jaffe	Director	EVL, ARC, NIDA												
COOPERATING UNITS (if any) The Johns Hopkins University (K.L. Preston); Biology of Vulnerability Chemistry and Drug Metabolism														
LAB/BRANCH Clinical Biology Branch														
SECTION Biology of Dependence and Abuse Potential Assessment Laboratory														
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224														
TOTAL MAN-YEARS: 0.90	PROFESSIONAL: 0.40	OTHER: 0.50												
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews														
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Following from observations that post-addicts and non-opioid users are differentially sensitive to opioids, and perhaps even respond qualitatively differently, as well as the possibility that such differences either predispose certain persons to opioid abuse and/or contribute to relapse, this study was conducted to experimentally examine such population differences in response to mu and kappa opioids. Prominent measures included discrimination thresholds of behavioral effects, physiologic responses, and neuroendocrine responses. Post-addict and opioid-naive subjects were intended to be separately tested for comparison. Testing is completed; however, upon the initial phase involving post-addict volunteers, changes in priorities resulted in the termination of the protocol before opioid-naive subjects were tested. Initial results suggest that a single dose of morphine is sufficient to measure a mild withdrawal-like effect when the opioid antagonist, naloxone, is subsequently administered.</p> <p><b>Publication</b></p> <p>Higgins, S.T., Preston, K.L., Cone, E.J., Henningfield, J.E. and Jaffe, J.H.: Behavioral, Physiological and Hormonal Effects of a Naloxone Challenge Following Acute Morphine Pretreatment in Humans. In Harris, L.S. (Ed.): <u>NIDA Research Monograph 76</u>. Washington, DC, U.S. Government Printing Office, 1987, pp. 266-273.</p>														



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00013-04 BDL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Archival Database Project

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C. Haertzen	Research Psychologist	BDL, ARC, NIDA
Others: J.E. Henningfield	Chief	BDL, ARC, NIDA
W.R. Lange	Medical Officer	RSB, ARC, NIDA
J.H. Jaffe	Director	ARC, NIDA
F.R. Snyder	Statistician	CHP, ARC, NIDA

COOPERATING UNITS (if any)

Research Support Branch; Biology of Vulnerability Laboratory  
Cognitive Studies and Human Performance Laboratory

LAB/BRANCH

Clinical Biology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.12

PROFESSIONAL:

0.62

OTHER:

0.50

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Currently data obtained by the recruitment staff (i.e., Addiction Severity Index, Symptom Checklist [SCL-90], Shipley IQ, Early Childhood Aggression) and admission test data (i.e., Diagnostic Interview Schedule, Buss-Durkee Hostility, Minnesota Multiphasic Personality Inventory [MMPI], Alcohol Related Behavioral Questionnaire, and electroencephalogram) have been combined into a single database. The results of the analyses will be reported by those in the Psychology of Vulnerability Laboratory. One finding of particular interest concerned hostility (i.e., assault) which is related to antisocial personality. For example, a database comprised of 97 opiate addicts given the Addiction Research Center Inventory (ARCI) under no-drug and morphine (20 mg i.m.) conditions and the MMPI under a non-drug condition was assembled. Interest in this database was focused on the question of whether a high level of hostility constituted a risk factor for feeling greater morphine effects. Hostility was positively related to four morphine-related scales. Further, those high on hostility had twice the change in elevation on a simulated opiate scale as those who were low. This database has been extended to include a wide range of other psychoactive drugs. Another finding concerned the prevalence of nitrite use. Nitrite use was more common in a sample of alcoholics in treatment (22%) than in drug abusers. A number of papers were derived in part from the Admission Database which is comprised of many tests.

Z01 DA00013-04 BDL (Cont'd)

## Archival Database Project

### Publications

Haertzen, C.A. and Hickey, J.E.: Addiction Research Center Inventory (ARCI): Measurement of Euphoria and Other Drug Effects. In Bozarth, M.A. (Ed.): Methods of Assessing the Reinforcing Properties of Abused Drugs. New York, NY, Springer-Verlag, 1987, pp. 489-524.

Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M. and Jaffe, J.H.: Nitrite inhalants: Patterns of abuse in Baltimore and Washington, D.C. Am. J. Drug Alcohol Abuse 14: 29-39, 1988.

### Papers Under Review

Haertzen, C.A., Hickey, J.E., Rose, M.R. and Jaffe, J.H.: The relationship between a diagnosis of antisocial personality and hostility: Development of an antisocial hostility scale.

Fishbein, D.H., Herning, R.I., Pickworth, W.B., Haertzen, C.A., Hickey, J.E. and Jaffe, J.H.: Brainstem evoked response potentials in adult male drug abusers with self-reported histories of aggressive behavior.

Rose, M.R., Brown, B.S. and Haertzen, C.A.: Comparison of the characteristics and functioning of cocaine treatment and cocaine research subjects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  Z01 DA00014-02 BDL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cholinergic Agonists and Antagonists (Army Contract-Related)		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: J.E. Henningfield	Chief	BDL, ARC, NIDA
Others: J.D. Roche	Staff Fellow	BDL, ARC, NIDA
W.R. Lange	Medical Officer	RSB, ARC, NIDA
R.I. Herning	Chief	CHP, ARC, NIDA
W.B. Pickworth	Pharmacologist	CHP, ARC, NIDA
COOPERATING UNITS (if any) Research Support Branch Cognitive Studies and Human Performance Laboratory		
LAB/BRANCH Clinical Biology Branch		
SECTION Biology of Dependence and Abuse Potential Assessment Laboratory		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.70	PROFESSIONAL: 0.20	OTHER: 0.50
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)  Human volunteers without histories of drug abuse, except for cigarette smoking, were tested to assess the possible adverse performance effects of a cholinergic agonist and antagonist, given singly and in combination. A dose run-up procedure was conducted with the cholinergic agonist, physostigmine, to determine a dose which may be safely given but, at which, reliable behavioral and physiologic effects are observed. The anticholinergic, methscopolamine, was then given to assess the degree to which non-central blockade reduces physiological effects and/or performance impairment. The Army Performance Assessment Battery (PAB), including components of the Triservices PAB, was used to evaluate behavioral performance. Exploratory testing has been completed.		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER <b>Z01 DA00024-02 BDL</b>																								
PERIOD COVERED <b>October 1, 1987 to December 31, 1988</b>																										
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Opioid Self-Administration: Humans Compared to Animals</b>																										
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">PI: J.E. Henningfield</td> <td style="width: 30%;">Chief</td> <td style="width: 40%;">BDL, ARC, NIDA</td> </tr> <tr> <td>Others: S.J. Heishman</td> <td>Staff Fellow</td> <td>BDL, ARC, NIDA</td> </tr> <tr> <td>R.L. Lamb</td> <td>Staff Fellow</td> <td>BDL, ARC, NIDA</td> </tr> <tr> <td>S.R. Goldberg</td> <td>Chief</td> <td>BPL, ARC, NIDA</td> </tr> <tr> <td>J.L. Katz</td> <td>Staff Fellow</td> <td>BPL, ARC, NIDA</td> </tr> <tr> <td>C.W. Schindler</td> <td>Staff Fellow</td> <td>BPL, ARC, NIDA</td> </tr> <tr> <td>W.R. Lange</td> <td>Medical Officer</td> <td>RSB, ARC, NIDA</td> </tr> <tr> <td>R.A. Meisch</td> <td>Visiting Scientist</td> <td>BDL, ARC, NIDA</td> </tr> </table>			PI: J.E. Henningfield	Chief	BDL, ARC, NIDA	Others: S.J. Heishman	Staff Fellow	BDL, ARC, NIDA	R.L. Lamb	Staff Fellow	BDL, ARC, NIDA	S.R. Goldberg	Chief	BPL, ARC, NIDA	J.L. Katz	Staff Fellow	BPL, ARC, NIDA	C.W. Schindler	Staff Fellow	BPL, ARC, NIDA	W.R. Lange	Medical Officer	RSB, ARC, NIDA	R.A. Meisch	Visiting Scientist	BDL, ARC, NIDA
PI: J.E. Henningfield	Chief	BDL, ARC, NIDA																								
Others: S.J. Heishman	Staff Fellow	BDL, ARC, NIDA																								
R.L. Lamb	Staff Fellow	BDL, ARC, NIDA																								
S.R. Goldberg	Chief	BPL, ARC, NIDA																								
J.L. Katz	Staff Fellow	BPL, ARC, NIDA																								
C.W. Schindler	Staff Fellow	BPL, ARC, NIDA																								
W.R. Lange	Medical Officer	RSB, ARC, NIDA																								
R.A. Meisch	Visiting Scientist	BDL, ARC, NIDA																								
COOPERATING UNITS (if any) Behavioral Pharmacology Laboratory Research Support Branch, U. of Minnesota (R.A. Meisch)																										
LAB/BRANCH Clinical Biology Branch																										
SECTION Biology of Dependence and Abuse Potential Assessment Laboratory																										
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224																										
TOTAL MAN-YEARS: <div style="text-align: center;">0.15</div>	PROFESSIONAL: <div style="text-align: center;">0.10</div>	OTHER: <div style="text-align: center;">0.05</div>																								
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews																										
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Studies with animals have shown that stimuli associated with drug delivery can come to function as variables that partially control drug-seeking behavior and the likelihood of resumption (i.e., relapse) of such behavior, even in the absence of the drug. Analogous research strategies are being used to assess the generality of these findings to human subjects. In addition, these procedures provide data on the degree of correspondence between self-reported drug effects and drug-seeking behavior. The human studies have produced a number of interesting results. When the consequences of varying the dose of morphine available on self-administration, physiological effects, and self-reported effects were examined, it was found that low doses of morphine (3.75 mg) maintained rates of responding above placebo and constricted pupillary diameter, but did not reliably alter the self-reports of the subjects, indicating a dissociation between the subjective effects of morphine and morphine's reinforcing properties. Another study evaluated the role of a stimuli paired with drug administration on the maintenance of responding. Initial results suggested that the stimuli were of less importance than in an analogous study with animals, as well as in a somewhat similar study of cocaine self-administration by humans. The basis for these differences is currently under investigation.</p>																										



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  Z01 DA00025-02 BDL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Acquisition of Dependence to Cigarettes and Smokeless Tobacco		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.E. Henningfield	Chief BDL, ARC, NIDA
Others:	R. Nemeth-Coslett	Staff Fellow BDL, ARC, NIDA
	E.J. Cone	Chief CDM, ARC, NIDA
	C.A. Haertzen	Research Psychologist BDL, ARC, NIDA
	F.R. Snyder	Statistician CHP, ARC, NIDA
	A. Radzius	Research Assistant BDL, ARC, NIDA
	W.R. Lange	Medical Officer RSB, ARC, NIDA
COOPERATING UNITS (if any) Dr. J. Grabowski (U. of Texas Health Science Center, Houston); Dr. K.O. Fagerstrom (Pharmacia LEO Therapeutics AB; Helsingborg, Sweden)		
LAB/BRANCH Clinical Biology Branch		
SECTION Biology of Dependence and Abuse Potential Assessment Laboratory		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.50	0.25	0.25
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Questionnaires were given to populations of experienced cigarette and/or smokeless tobacco users (785 responses), and to a population which included persons who had never used tobacco (496 responses). The purpose of the questionnaires was to determine changes in the amount of tobacco products consumed as a function of time, and to assess the level of nicotine dependence, as measured by the Fagerstrom Tolerance Questionnaire (FTQ). Findings that have emerged from initial analysis of the first population include the following: (1) Smokeless tobacco use begins about one year earlier than cigarette use (15.5 versus 16.3 years); (2) Males begin smoking about one year earlier than females; (3) Tobacco consumption increased over time (i.e., dose graduation); (4) The dose escalation was negatively accelerated with no difference between sexes; (5) Age of starting smoking is negatively correlated with the age of quitting and also with predicted FTQ scores after the same number of years of smoking; (6) Four of 8 questions on the FTQ scale are correlated with total FTQ score. Analyses in progress are: (1) Analysis of brands smoked; (2) Prediction of dependence based on the amount of tobacco product consumed at some early point in history; and, (3) Analysis of the data from the 496 response population. These data need only to undergo final analyses before publication.		

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE</b> <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>	<b>PROJECT NUMBER</b>  <b>Z01 DA00026-01 BDL</b>
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PERIOD COVERED  
**October 1, 1987 to December 31, 1988**

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
**Assessment of Opioid Agonists and Antagonists**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	S.J. Heishman	Staff Fellow	BDL, ARC, NIDA
	E.J. Cone	Chief	CDM, ARC, NIDA
	R.E. Johnson	Chief	RSB, ARC, NIDA
	P.J. Fudala	Deputy Chief	RSB, ARC, NIDA

COOPERATING UNITS (if any)  
**Chemistry & Drug Metabolism Laboratory**  
**Research Support Branch**

LAB/BRANCH  
**Clinical Biology Branch**

SECTION

INSTITUTE AND LOCATION  
**Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224**

TOTAL MAN-YEARS: <b>1.10</b>	PROFESSIONAL: <b>0.40</b>	OTHER: <b>0.70</b>
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CHECK APPROPRIATE BOX(ES)  
☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Subjects with histories of opioid abuse were studied on the Residential Research Unit to determine the possible abuse potential of nalmefene, a new investigational opioid antagonist with relatively few agonist effects. The efficacy of nalmefene in blocking the effects of morphine was also evaluated. Blood samples taken over time were analyzed to provide an assessment of the relationship between the effects of nalmefene and its plasma levels as well as those of its metabolites. The results of this study may be useful in determining the possible utility of this long-acting (i.e., possibly several days) opioid antagonist for the treatment of opioid dependent persons. This study is being done in collaboration with the Chemistry and Drug Metabolism Laboratory and the Research Support Branch; preliminary subject testing has begun.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00027-01 BDL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Psychotropic Properties of Stimulants and Sedatives: Discriminative Properties		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.E. Henningfield      Chief	BDL, ARC, NIDA
Others:	S.J. Heishman      Staff Fellow	BDL, ARC, NIDA
	R.J. Lamb      Staff Fellow	BDL, ARC, NIDA
	W.R. Lange      Medical Officer	RSB, ARC, NIDA
COOPERATING UNITS (if any) Research Support Branch		
LAB/BRANCH Clinical Biology Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.85	0.25	0.60
CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither		
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
<p>Subjects with histories of stimulant and sedative abuse are studied on the Residential Research Unit to determine their ability to discriminate between prototypic stimulants and sedatives using both traditional subjective effects and measures of behavioral discrimination. An opioid may also be evaluated in some tests involving subjects with histories of opioid abuse. This study may help to improve the accuracy of this Laboratory's procedures for assessing abuse liability by quantitatively assessing similarities and differences among drugs based upon controlled exposure to human volunteers. This study may also generate a base of data developed in human volunteers which may be compared to the extensive amount of data that has been collected using animal subjects. Subject testing has begun.</p>		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00028-01 BDL
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Assessment of Mazindol for Abuse Liability

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	S.A. Klein	Staff Fellow	BDL, ARC, NIDA
	M.J. Kuhar	Chief	MPL, ARC, NIDA

COOPERATING UNITS (if any)  
Molecular Pharmacology Laboratory

LAB/BRANCH  
Clinical Pharmacology Branch

SECTION

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.65	PROFESSIONAL: 0.30	OTHER: 0.35
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CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Subjects with histories of stimulant abuse are being studied on the Residential Unit to compare the abuse liability of mazindol (an anorectic agent with some psychomotor stimulant properties) to methylphenidate (a prototypic psychomotor stimulant with known potential for abuse). This study was performed since mazindol has been used in binding studies whose goal was to isolate the cocaine receptor. Moreover, mazindol is a theoretically interesting drug since its apparent mechanism of action, which involves blocking the reuptake of norepinephrine and dopamine, would suggest that one might expect it to exhibit some abuse liability. Despite this, one previous study and limited clinical experience suggest that any abuse liability associated with mazindol is not substantial. Therefore, additional characterization of the clinical pharmacology of mazindol could be of definite use in analytic efforts designed to dissect out the properties of various stimulant agents, as well as for drug development efforts. This study is being conducted in collaboration with the Neuroscience Branch; subject testing has begun.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA00029-01 BDL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Interaction Between Ethanol and Prostaglandin Synthetase Inhibitors</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: J.E. Henningfield	Chief	BDL, ARC, NIDA
Others: S.A. Klein	Staff Fellow	BDL, ARC, NIDA
F.R. George	Staff Fellow	PPB, ARC, NIDA
COOPERATING UNITS (if any) Preclinical Biology Branch		
LAB/BRANCH Clinical Pharmacology Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.65	PROFESSIONAL: 0.30	OTHER: 0.35
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Subjects with histories of moderate alcohol use are studied on the Residential Research Unit to assess the effects of ethanol following pretreatment with either acetaminophen or placebo. Acetaminophen is a prostaglandin synthetase inhibitor that has been shown to reduce several behavioral and physiologic effects of alcohol in animal studies. Alcohol appears to act in part by increasing prostaglandin levels. This drug interaction study makes use of this Laboratory's standard procedures for assessing abuse potential and performance to evaluate the possibility of such antagonistic effects in human subjects. This study is conducted in collaboration with the Preclinical Branch; subject testing has begun.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00030-01 BDL
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PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Passive Tobacco Smoke: Nicotine Absorption, Subjective Effects, and Performance		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) PI: J.E. Henningfield Chief BDL, ARC, NIDA  Others: P.W. Woodson Staff Fellow BDL, ARC, NIDA J.D. Roache Staff Fellow BDL, ARC, NIDA		

COOPERATING UNITS (if any) None
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LAB/BRANCH Clinical Biology Branch
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SECTION
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
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TOTAL MAN-YEARS: 0.35	PROFESSIONAL: 0.15	OTHER: 0.20
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CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
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SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)
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Three subject groups are being compared in a study of the effects of exposure to ambient tobacco smoke, generated by a cigarette smoking machine, on standard measures of subjective and physiologic effects as well as on performance. The groups are: nondeprived cigarette smokers, 12-hour smoke-deprived cigarette smokers, and nonsmokers. It is hoped that the use of the performance battery included in this study will provide a quantitative assay by which to determine if various ambient levels of tobacco smoke can produce dose-dependent effects on performance and physiology which are comparable to those observed with cigarette smoking. Initial research demonstrated the safety and reliability of the procedures used to induce passive tobacco smoke exposure. Further testing is continuing as resources permit.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00031-01 BDL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effects of Nicotine in Nonsmokers

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J.E. Henningfield Chief BDL, ARC, NIDA

Others: S.J. Heishman Staff Fellow BDL, ARC, NIDA  
F.R. Snyder Statistician CHP, ARC, NIDA

## COOPERATING UNITS (if any)

Biology of Vulnerability Laboratory

## LAB/BRANCH

Clinical Biology Branch

## SECTION

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.10

## PROFESSIONAL:

0.30

## OTHER:

0.80

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Nonsmokers are exposed to nicotine given in the form of nicotine polacrilex gum; preliminary testing suggests that this formulation is of low abuse liability and is safe if given according to proscribed procedures. Two important experimental questions are addressed in this study. One concerns the further evaluation of the effects of nicotine polacrilex gum in nonsmokers to determine the possible effects of nicotine on cognitive performance in the absence of pre-existing nicotine dependence. Nicotine enhances performance in deprived smokers; however, it remains to be determined if nicotine dependence is a precondition for this effect. The second question is of general importance to the understanding of the development of drug dependence. Using a model of daily repeated voluntary cumulative dosing, the course of possible development of tolerance to the subjective, behavioral and physiologic actions of nicotine will be determined. Such data cannot be readily obtained with other drugs of abuse, and probably not with forms of nicotine known to be of high abuse liability (e.g., cigarettes), but may be safely collected following the procedures used in this study. A preliminary study was completed and the more extensive protocol has been initiated.





**Biology and Psychology of Vulnerability Laboratories — Jerome H. Jaffe,  
M.D., Acting Chief**

**Overview**

These Laboratories were established to conduct studies of individual differences in acute responses to abused drugs (i.e., reinforcing effects) and to examine the mechanisms involved in those factors known to be associated with later drug abuse problems: male gender, childhood aggression, antisocial personality, and biological parents with a history of alcoholism or criminality. In addition, these Laboratories assumed the major burden of initiating clinical studies of cocaine at the ARC. For most of the period covered by this report, the scientific staff of the Laboratory of Biology of Vulnerability consisted of one staff scientist, Dr. Karen M. Kumor and one staff fellow, Dr. Carlos Muntaner. This Laboratory has worked so closely with the Laboratory of Psychology of Vulnerability that these laboratories essentially function as a single unit. The Psychology of Vulnerability Laboratory consisted of one staff member, Dr. David Newlin, and two fellows, Drs. Craig Nagoshi and Diana Fishbein. A merger of the two laboratories in the next fiscal year is likely. A small preclinical unit with one staff member (Dr. Larry Sharpe) has been collaborating on the effects of calcium channel blockers, dopaminergic blockers, and carbamazepine on the reinforcing effects of cocaine. The Section on Neuroendocrinology and Immunology, headed by Dr. Elizabeth Dax, formed in the previous year, has become an independent laboratory within the Branch during the year; the diverse activities of this group are described in a separate section of this report.

**Summary of Ongoing Research**

During the past year, the Laboratories of the Biology and Psychology of Vulnerability conducted studies in several areas including:

**I. Clinical Studies**

**A. Interactions of Cocaine and Other Psychoactive Agents.**

1. Studies of the Neurotransmitter(s) Involved in the Effects of Cocaine Using Haloperidol and Bromocriptine;
2. Interactions of Cocaine and Calcium Channel Blockers.

**B. Differences in Serotonergic Sensitivity among Former Drug Users with High and Low Levels of Self-Reported Aggressive Behavior (The Serotonin Project).**

- C. Effects of Conditioning on Acute Tolerance to Morphine.
- D. Electrophysiological and Psychological Characteristics of Subjects Admitted to the Addiction Research Center (Database Project).

## II. Preclinical Studies

- A. Effects of Environmental Housing Conditions on Drug (Opioid) Self-Administration.
- B. Effects of Pretreatment with Calcium Channel Blockers and Other Agents Altering Dopaminergic Reinforcement Systems on Cocaine Self-Administration.
- C. Effects of Chronically Administered Cocaine on Pituitary Release of Hormones.
- D. Neurotoxic Effects of Chronically Administered Cocaine.

## Publications

Babor, T.F., Dolinsky, Z., Rounsaville, B. and Jaffe, J.H.: Unitary versus multidimensional models of alcoholism treatment outcome: An empirical study. J. Stud. Alcohol 49: 167-177, 1988.

Cascella, N., Muntaner, C., Nagoshi, C.T., Kumor, K.M., Sherer, M.A. and Jaffe, J.H.: Cardiovascular responses to cocaine placebo in humans: A preliminary report. Biol. Psychiatry, In press.

Ciraulo, D.A., Barnhill, J.G. and Jaffe, J.H.: Clinical pharmacokinetics of imipramine and desipramine in alcoholics and normal volunteers. Clin. Pharmacol. Ther. 43: 509-518, 1988.

Cone, E.J., Kumor, K.M., Thompson, L.K. and Sherer, M.A.: Correlation of saliva cocaine levels with plasma levels and with pharmacologic effects after intravenous cocaine administration in human subjects. J. Anal. Toxicol. 12: 200-206, 1988.

Herning, R.I., Hickey, J.E., Pickworth, W.B. and Jaffe, J.H.: Auditory event related potentials in adolescents at risk for drug abuse. Biol. Psychiatry, In press.

Fishbein, D.H., Herning, R.I., Pickworth, W.B., Haertzen, C.A., Hickey, J.E. and Jaffe, J.H.: Spontaneous EEG and brainstem evoked response potentials in drug abusers with histories of aggressive behavior. Biol. Psychiatry, In press.

## Publications (Cont'd)

Thompson, L.K. and Cone, E.J.: Determination of delta-9-tetrahydrocannabinol in human blood and saliva by high performance liquid chromatography with amperometric detection. J. Chromatogr. 421: 91-97, 1987.

Cone, E.J., Welch, P. and Lange, W.R.: Clonidine partially blocks the physiologic effects but not the subjective effects produced by smoking marijuana in male human subjects. Pharmacol. Biochem. Beh. 29: 649-652, 1988.

Cone, E.J., Johnson, R.E., Paul, B.D., Mell, L.D. and Mitchell, J.: Marijuana-laced brownies: Behavioral effects, physiologic effects and urinalysis in humans following ingestion. J. Anal. Toxicol. 12: 169-175, 1988.

Fishbein, D.H., Lozovsky, D. and Jaffe, J.H.: Neuroendocrine responses to a serotonergic probe in substance users with different levels of aggressiveness and impulsivity. Biol. Psychiatry, In press.

Jaffe, J.H.: Biological Risk Factors in Alcoholism: Overview. In J.R. Rose and J. Barrett (Eds.): Alcoholism: Origins and Outcome. New York, NY, Raven Press, 1988, pp. 229-235.

Jaffe, J.H., Babor, T.F. and Fishbein, D.H.: Alcoholics, aggression and antisocial personality. J. Stud. Alcohol 49(3): 211-218, 1988.

Jaffe, J.H., Cascella, N.G., Kumor, K.M. and Sherer, M.A.: Cocaine-induced cocaine craving. Psychopharmacology, In press.

Jaffe, J.H.: Misinformation: Euphoria and Addiction. In Hill, C.S. and Fields, W.W. (Eds.): Advances in Pain Research and Therapy. New York, NY, Raven Press, In press.

Jaffe, J.H. and Jaffe, F.K.: Historical Perspectives on the Use of Subjective Effects Measures in Assessing the Abuse Potential of Drugs. In Human Testing for Drug Misuse and Abuse Liability, In press.

Jaffe, J.H.: Addictions: What does biology have to tell? Int. Rev. J. Psychiat., In press.

Jaffe, J.H.: Opioid Detoxification. In: Report of the American Psychological Association's Task Force on Treatments of Psychiatric Disorders. Washington, DC, APA Press, In press.



## Publications (Cont'd)

Thompson, L.K. and Cone, E.J.: Determination of delta-9-tetrahydrocannabinol in human blood and saliva by high performance liquid chromatography with amperometric detection. J. Chromatogr. 421: 91-97, 1987.

Cone, E.J., Welch, P. and Lange, W.R.: Clonidine partially blocks the physiologic effects but not the subjective effects produced by smoking marijuana in male human subjects. Pharmacol. Biochem. Beh. 29: 649-652, 1988.

Cone, E.J., Johnson, R.E., Paul, B.D., Mell, L.D. and Mitchell, J.: Marijuana-laced brownies: Behavioral effects, physiologic effects and urinalysis in humans following ingestion. J. Anal. Toxicol. 12: 169-175, 1988.

Jaffe, J.H.: Psychoactive Substance Use Disorders. In: Comprehensive Textbook of Psychiatry, Fifth Edition. Baltimore, MD, Williams & Wilkins, In press.

Kumor, K.M., Haertzen, C.A., Jasinski, D.R. and Johnson, R.E.: The psychopharmacologic and prolactin response after large doses of naloxone. Pharmacol. Biochem. Behav. 30: 967-975, 1988.

Kumor, K.M., Sherer, M.A., Thompson, L.K., Cone, E.J., Mahaffey, J. and Jaffe, J.H.: Lack of cardiovascular tolerance during intravenous infusions of cocaine in man. Life Sci. 42: 2063-3071, 1988.

Kumor, K.M., Sherer, M.A., Gomez, J., Cone, E.J. and Jaffe, J.H.: Subjective responses during continuous infusion of cocaine. Pharmacology, In press.

Kumor, K.M., Sherer, M.A., and Cascella, N.G.: Cocaine Use in Man: Subjective Effects, Physiologic Responses and Toxicity. In Cocaine, Marijuana, Designer Drugs: Chemistry, Pharmacology, and Behavior. Cleveland, OH, CRC Press, In press.

Kumor, K.M., Conklin, R., Woo, J., Katz, L. and Strocchia, C.: Renal function studies during intravenous acyclovir treatment of immune-suppressed patients including renal transplantation. Amer. J. Nephrol. 8: 35-39, 1988.

Sherer, M.A., Kumor, K.M., Cone, E.J. and Jaffe, J.H.: Suspiciousness induced by four-hour intravenous infusions of cocaine - preliminary findings. Arch. Gen. Psychiatry 45: 673-677, 1988.

Sherer, M.A., Kumor, K.M. and Jaffe, J.H.: Effects of intravenous cocaine are partially attenuated by haloperidol. Psychiatry Res., In press.



## Abstracts

Fishbein, D.H., Lozovsky, D. and Jaffe, J.H.: Neuroendocrine responses to a serotonergic probe and glucose challenge in substance users with different levels of aggressiveness and impulsivity. American College of Neuropsychopharmacology. Puerto Rico, November 1987.

Jaffe, J.H., Kumor, K.M., Itil, T.M. and Itil, K.Z.: XVth Collegium Internationale Neuropsychopharmacologicum. Frankfurt, West Germany, August 1988.

Kumor, K.M., Sherer, M.A., Muntaner, C., Jaffe, J.H. and Herning, R.I.: Pharmacologic aspects of cocaine rush. Committee on Problems of Drug Dependence. N. Falmouth, MA, June 1988.

Muntaner, C., Kumor, K.M. and Jaffe, J.H.: Effects of nifedipine (a calcium modulator) pretreatment on cardiovascular and subjective responses to intravenous cocaine administration in humans. Committee on Problems of Drug Dependence. N. Falmouth, MA, June 1988.

Newlin, D.B.: A response completed model of tolerance and sensitization. Committee on Problems of Drug Dependence. N. Falmouth, MA, June 1988.

Newlin, D.B. and Thomson, J.B.: Sensitization to alcohol in sons of alcoholics: A replication study. Annual Meeting of the Research Society on Alcoholism. Isle of Palms, SC, June 1988.

Sharpe, L.G. and Jaffe, J.H.: Modification of naloxone-precipitated withdrawal signs by captopril and capsaicin in the morphine-dependent rat. 17th Annual Meeting, Society for Neuroscience. New Orleans, LA, November 1987.

Sharpe, L.G., Jaffe, J.H. and Jaffe, A.B.: Rats rapidly learn to self-administer sufentanil in aerosol form. Committee on Problems of Drug Dependence. N. Falmouth, MA, June 1988.

## Other

Fishbein, D.H. and Pease, S.E.: The Theory, Practice and Evaluation of Behavioral Change as a Function of Dietary Intervention: Implications for Criminology and Corrections. The Rand Corporation and National Institute for Corrections Monograph Series. May 1988.

Fernandez, A., Roca, M., Ugarte, B. and Muntaner, C.: Asthma and psychosocial variables. Psiquis 9: 30-36, 1988.

Other (Cont'd)

Kimes, A., Kumor, K.M., McCullough, K., Holtzclaw, D., Teller, D., Dobyan, D. and Spector, D.: Effects of acute and chronic acyclovir on canine renal function. J. Pharmacol. Exp. Therap., In press.

Muntaner, C., Sevilla, L.G., Fernandez, A. and Torrubia, J.: Personality dimensions, schizotypal and borderline personality traits and psychosis proneness. Personality and Individual Differences 9: 257-268, 1988.

Newlin, D.B.: Placebo responding in the same direction as alcohol in women. Alcoholism, In press.

Newlin, D.B., Hotchkiss, B., Cox, W.M., Rauscher, F. and Li, T.K.: Autonomic and subjective responses to alcohol with appropriate control stimuli. Addict. Behav., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00101-01 BPVL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Measures of Psychopathology and Personality as Predictors of Substance Abuse		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.H. Jaffe	Acting Chief BPVL, ARC, NIDA
Others:	C. Muntaner	Visiting Fellow BPVL, ARC, NIDA
	C. Nagoshi	Staff Fellow BPVL, ARC, NIDA
	C. Haertzen	Staff Psychologist BDP, ARC, NIDA
	D. Fishbein	Staff Fellow BPVL, ARC, NIDA
COOPERATING UNITS (if any) None		
LAB/BRANCH Biology and Psychology of Vulnerability Laboratories		
SECTION Clinical Pharmacology		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 3.00	PROFESSIONAL: 1.00	OTHER: 2.00
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  There is a large body of literature on the association of alcohol and drug use, abuse and dependence with psychopathology, including depression and antisocial personality disorder, as well as with aspects of normal personality, such as impulsiveness. Differences in personality have been important in defining qualitatively different subpopulations of substance abusers, e.g., Type I versus Type II alcoholics. Subjects volunteering for research and treatment studies at the ARC represent a unique sample of urban drug users that may be studied extensively to ascertain demographic and psychological predictors of substance abuse, to replicate previous findings, and to develop new measures and lines of inquiry. The psychological data obtained may also be useful in understanding the results of drug effect and treatment outcome studies.  At present, inpatients are being assessed on measures of lifetime and current psychopathology, normal personality, impulsiveness, sensation-seeking, hostility, lifetime criminality, early childhood aggression, intelligence, demographic variables, and lifetime and current drug use, abuse, and dependence. Analyses have been completed on measures of aggression as predictors of drug dependence, on the construct validity of a measure of early childhood aggression, and on expectancies of hostility while intoxicated as a predictor of drug dependence.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00102-01 BPVL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Serotonergic Activity in Drug Abusers: Relationship to Indices of Aggressiveness		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.H. Jaffe	Acting Chief
Others:	D.H. Fishbein	Staff Fellow
	C. Contorregi	Staff Fellow
	E.M. Dax	Chief
	R.I. Herning	Chief
	C.T. Nagoshi	Staff Fellow
	A. Weissman	Staff Fellow
		BPVL, ARC, NIDA
		BPVL, ARC, NIDA
		BPVL, ARC, NIDA
		NEI, ARC, NIDA
		CHP, ARC, NIDA
		BPVL, ARC, NIDA
		BPVL, ARC, NIDA
COOPERATING UNITS (if any) Cognitive Studies & Human Performance Laboratory Neuroendocrinology/Immunology Laboratory		
LAB/BRANCH Biology and Psychology of Vulnerability Laboratories		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.60	PROFESSIONAL: 0.30	OTHER: 0.30
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Subjects volunteering for studies at the ARC who are not actively dependent on any agent other than nicotine are given an extensive psychological test battery, including several personality tests and specialized tests of self-reported aggression. In addition, baseline endocrine measures and platelet receptor binding affinity for serotonergic agents are evaluated; spontaneous EEG and brain evoked potential measures are obtained at baseline and following the administration of a single dose of fenfluramine. Neuroendocrine responses to fenfluramine are also measured.</p> <p>The major hypothesis being tested is that subjects who differ in terms of aggression and impulsivity will also differ in terms of serotonergic function and will respond differently to serotonergic agents. Further, it is hypothesized that the diagnosis of antisocial personality using the Diagnostic and Statistical Manual, Third Edition (DSM-III) criteria will not necessarily predict these responses independently of measures of aggression and impulsivity.</p>		



Z01 DA00102-01 BPVL (Cont'd)

**Serotonergic Activity in Drug Abusers: Relationship to Indices of Aggressiveness**

To date, more than 40 subjects have been studied. In the first 25 who were selected for extreme scores on self-reported measures of aggression and hostility, a correlation was found between both peak prolactin levels and cortisol responses to fenfluramine and the self-reported measures of aggression and hostility.

**Publication**

Fishbein, D.H., Lozovski, D. and Jaffe, J.H.: Neuroendocrine responses to a serotonergic probe in substance users with different levels of aggressiveness and impulsivity. Biol. Psychiatry, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA00103-01 BPVL
PERIOD COVERED <b>October 1, 1987 to December 31, 1988</b>		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Pavlovian Conditioning to Morphine in Opiate Abusers</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:        D.B. Newlin	Research Psychologist	BPVL, ARC, NIDA
Others: M.B. Pretorius J.H. Jaffe	Psychologist Associate Acting Chief	BPVL, ARC, NIDA BPVL, ARC, NIDA
COOPERATING UNITS (if any) None		
LAB/BRANCH <b>Biology and Psychology of Vulnerability Laboratories</b>		
SECTION <b>Clinical Pharmacology</b>		
INSTITUTE AND LOCATION <b>Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224</b>		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
<p>Previous demonstrations of conditioned responses to opiate cues in humans have not involved opiate conditioning trials in the laboratory. This experiment provided direct evidence of Pavlovian conditioning to morphine in a highly distinctive laboratory environment that was explicitly paired with opiate administration, and in a novel environment that was not associated with the drug. In a modification of experimental designs used in the animal literature, 10 men with a history of opiate use participated in a within-subject, repeated-measures experiment involving 7 sessions on alternate days. In the first session, subjects became familiar with the laboratory, but received no injection. In the next four sessions, they received morphine (20 mg i.m.) in a distinctive laboratory environment; in the sixth session, they received a placebo injection in the morphine-associated environment, and in the seventh session they received the same dose of morphine in a novel environment.</p> <p>Significant tolerance developed to the hypothermia and negative affect measured by the Profile of Mood States (POMS) measure; sensitization developed to a measure of analgesia. Notably, the placebo response was opposite in direction to the morphine effect for heart rate and cheek temperature. In contrast, the placebo response was in the same direction as drug for general motor activity, analgesia, static ataxia, and POMS-measured negative affect. There was some evidence of environmental specificity for tolerance development. These results indicate that morphine can be conditioned in the laboratory in humans; however, the results do not necessarily follow the predictions of Siegel's (1975) Pavlovian conditioning model.</p>		

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00104-01 BPVL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Role of Conditioning and Novelty in the Laboratory Response to Cocaine

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J.H. Jaffe Acting Chief BPVL, ARC, NIDA

Others: C. Muntaner Visiting Fellow BPVL, ARC, NIDA

K. M. Kumor Clinical Pharmacologist BPVL, ARC, NIDA

## COOPERATING UNITS (if any)

None

## LAB/BRANCH

Biology and Psychology of Vulnerability Laboratories

## SECTION

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.30

## PROFESSIONAL:

0.30

## OTHER:

0.00

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In the past several years, the ARC has been engaged in studying the interaction of cocaine with drugs which may have therapeutic value. These studies require valid assay systems for measuring the effects of drugs on the body and brain. Therefore, it is imperative that factors, such as subjects being aware of their drug or non-drug condition, be examined to determine if they affect the ultimate response. Hence, this study compared responses to a placebo administered after several single double-blind doses of cocaine on successive days to responses to a placebo in a situation in which subjects were told that they would receive placebo. The data reveal that the responses differ depending upon whether the subjects were aware of the treatment condition. Moreover, the data suggest the presence of a conditioned response. Further, evidence has been accumulated which suggests that a novelty or psychophysical scaling response exists during the initial doses of cocaine in a laboratory setting. These findings point to important methodological issues which it is crucial to take into consideration in study designs to adequately control for variables which may impact the outcome, and thus, to make it possible to draw inferences using a minimal number of subjects.

## Publications

Casella, N., Muntaner, C., Kumor, K.M., Sherer, M. and Jaffe, J.H.: Cardiovascular responses to cocaine placebo in humans. Psychopharmacology, In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00105-01 BPVL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Screening Criteria for Selecting Therapeutic Agents for Cocaine Dependence</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	R.I. Herning	Chief CHP, ARC, NIDA
Others:	J.H. Jaffe	Acting Chief BPVL, ARC, NIDA
	K. Kumor	Clinical Pharmacologist BPVL, ARC, NIDA
	C. Muntaner	Visiting Fellow BPVL, ARC, NIDA
COOPERATING UNITS (if any) Cognitive Studies and Human Performance Laboratory		
LAB/BRANCH Biology and Psychology of Vulnerability Laboratories		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.45	PROFESSIONAL: 0.25	OTHER: 0.20
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>In pilot studies investigating the utility of a new technology for the surface mapping of EEG frequencies in man, it was observed that nifedipine, a calcium channel modulator, caused a decline in the amount of beta wave activity of the dominant hemisphere. Cocaine has been observed in several studies, both independently and at the ARC, to cause increases in beta activity. Moreover, preliminary studies indicate that the increase in beta activity after cocaine may be diminished by the pretreatment of nifedipine, a drug which this Laboratory has found may also partially block the subjective effect of cocaine.</p> <p>Ongoing studies are investigating the EEG responses to oral doses of nifedipine and other calcium channel modulators in a randomized, double-blind study to determine if beta activity does decrease after calcium channel blockers and to delineate the time course and the location of this effect. This information will be used to develop strategies for selecting agents which demonstrate central nervous system activity and for designing future studies examining the interaction of calcium channel modulators and cocaine.</p>		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00106-01 BPVL
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Investigation of the Cocaine-Blocking Properties of Nifedipine
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)			
PI:	J.H. Jaffe	Acting Chief	BPVL, ARC, NIDA
Others:	K.M. Kumor C. Muntaner C.T. Nagoshi	Clinical Pharmacologist Visiting Fellow Visiting Scientist	BPVL, ARC, NIDA BPVL, ARC, NIDA BPVL, ARC, NIDA

COOPERATING UNITS (if any) Cognitive Studies and Human Performance Laboratory
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LAB/BRANCH Biology and Psychology of Vulnerability Laboratories
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SECTION
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
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TOTAL MAN-YEARS: 3.00	PROFESSIONAL: 1.30	OTHER: 1.70
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CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
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The interaction of nifedipine with cocaine was studied in a double-blind, randomized study employing 8 human subjects and using a three-way analysis. Either nifedipine, at a dose of 10 mg, or placebo was given orally 20 minutes before an intravenous challenge of cocaine, at doses of 20 or 40 mg, or placebo control. Measures included EEG, heart rate, blood pressure, numerous subjective effects scales, including the Profile of Mood Scale (POMS), the Cocaine Sensitive Scale and Rushgraph Scale, as well as the Observers' Cocaine Sensitive Scale.

The results showed that nifedipine blocked cocaine-induced tachycardia as well as a selection of subjective effects which included the cocaine "rush, cocaine craving, and general sensations associated with cocaine measured with the General Effect Scale. These effects were greater at the higher dose of cocaine. Nifedipine alone decreased blood pressure and the scores for confusion and tension on the POMS subscales, indicating that nifedipine itself may possess some psychoactivity. It was concluded that nifedipine demonstrates properties which may be of therapeutic value in the setting of cocaine dependence treatment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER <b>Z01 DA00107-01 BPVL</b>
PERIOD COVERED <b>October 1, 1987 to December 31, 1988</b>		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Evaluation of the Interaction of Bromocriptine with Cocaine</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:        J.H. Jaffe	Acting Chief	BPVL, ARC, NIDA
Others: K.M. Kumor C. Muntaner R.I. Herning	Clinical Pharmacologist Visiting Fellow Chief	BPVL, ARC, NIDA BPVL, ARC, NIDA CHP, ARC, NIDA
COOPERATING UNITS (if any) <b>Cognitive Studies and Human Performance Laboratory</b>		
LAB/BRANCH <b>Biology and Psychology of Vulnerability Laboratories</b>		
SECTION		
INSTITUTE AND LOCATION <b>Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224</b>		
TOTAL MAN-YEARS: 0.20	PROFESSIONAL: 0.20	OTHER: 0.00
CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
<p>There is a large body of work which indicates that dopaminergic transmission may be important in cocaine's reinforcement of behavior. This suggests that drugs active at the site of dopaminergic transmission may have therapeutic utility for cocaine-dependent patients. Bromocriptine has been reported to have therapeutic benefit in the treatment of cocaine dependence in uncontrolled studies. Thus, this study investigated the effects of bromocriptine (0.5 and 5.0 mg) or placebo pretreatment 2 hours prior to injections of cocaine or placebo in a blinded, semi-random, crossover design study using 9 subjects.</p> <p>Bromocriptine pretreatment was associated with only minor alterations of the heart rate, blood pressure, and subjective effects induced by cocaine. However, cocaine-induced cocaine craving was diminished to a statistically significant extent. It is possible that bromocriptine may be effective against a broader range of cocaine effects if different dose levels or a different dosing interval are used. In addition, a state of dopamine depletion in the subjects studied may explain the lack of statistically significant activity observed against certain of cocaine's effects.</p> <p><b>Publication</b></p> <p>Jaffe, J.H., Cascella, N.G., Kumor, K.M. and Sherer, M.A.: Cocaine-induced cocaine craving. <u>Psychopharmacology</u>, In press.</p>		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00108-01 BPVL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Evaluation of the Interaction of Haloperidol with Cocaine		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between;"> <div>           PI: J.H. Jaffe             Others: K.M. Kumor                      C. Muntaner                      N. Pilotte         </div> <div>           Acting Chief             Clinical Pharmacologist            Visiting Fellow            Staff Fellow         </div> <div>           BPVL, ARC, NIDA             BPVL, ARC, NIDA            BPVL, ARC, NIDA            NEI, ARC, NIDA         </div> </div>		
COOPERATING UNITS (if any)  Neuroendocrinology and Immunology Laboratory		
LAB/BRANCH Biology and Psychology of Vulnerability Laboratories		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.70	PROFESSIONAL: 0.40	OTHER: 0.30
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>There is a large body of work suggesting that dopaminergic transmission is important in cocaine's reinforcement of behavior. In animal studies, dopaminergic blocking drugs have been found to block the discriminative stimuli associated with cocaine and to cause extinction of patterns of self-administration. This suggests that drugs of this type may have therapeutic utility for cocaine-dependent patients. Thus, haloperidol, a post-synaptic dopaminergic blocker, was studied. The results showed that haloperidol pretreatment, 20 minutes before an intravenous cocaine challenge, diminished the good feelings associated with the cocaine injection, but did not diminish the cocaine rush. It appears that the interval between administration of haloperidol and cocaine challenge may be an important variable in any interactions observed.</p> <p>Ongoing studies are investigating the outcome of administering haloperidol 90 minutes prior to a cocaine injection. The design is a randomized, double-blind, crossover study. The measures include physiologic parameters, subjective effects scales (i.e., the ARCI and Cocaine Sensitive Scales), and levels of hormones (i.e., adrenocorticotrophic hormone [ACTH], growth hormone, prolactin, and cortisol).</p> <p><b>Publication</b>          Sherer, M.A., Kumor, K.M. and Jaffe, J.H.: Effects of intravenous cocaine are partially attenuated by haloperidol. <u>Psychiatry Research</u>, In press.</p>		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00109-01 BPVL
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Alcohol Challenge Studies in Sons of Alcoholics: Critical Review and Analysis
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)  PI:        D.B. Newlin                      Research Psychologist                      BPVL, ARC, NIDA
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COOPERATING UNITS (if any) None
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LAB/BRANCH Biology and Psychology of Vulnerability Laboratories
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SECTION Clinical Pharmacology
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
--

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews
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SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  This project involves a review and analysis of the theoretical and methodological assumptions underlying studies in which individuals with and without familial alcoholism are compared with respect to the response to acute administration of alcohol. The major assumptions of this paradigm are that alcoholism has a substantial heritable component, and that a deviant response to alcohol in individuals with a family history of alcoholism reflects a psychobiological marker for the disorder.  A critical review of the genetic literature led to the conclusion that there is some evidence of partial genetic transmission of alcoholism, although there are many problems associated with the limited data that are available.
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**Alcohol Challenge Studies in Sons of Alcoholics: Critical Review and Analysis**

Further, this project reviews alcohol challenge studies with individuals at risk for alcoholism due to familial alcoholism and provides a methodological critique of the procedures reported in this literature. Finally, the suggestion is developed for a conceptual model of these data in which differences in the response to alcohol between family history-positive and family history-negative individuals may be understood in relation to differences in the psychological response between the ascending and descending limbs of the blood alcohol curve.

This "differentiator" model proposes that sons of alcoholics exhibit acute sensitization during the rising blood alcohol curve and acute tolerance during the falling curve. Therefore, family history-positive subjects may find alcohol more rewarding because the pleasurable, excitatory aspects of the ascending limb may be accentuated, and the depressant responses of anxiety and depression that predominate in the falling curve may be attenuated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00110-01 BPVL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Neural Substrates of Behavior Maintained by Intravenous Psychomotor Stimulants		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: L.G. Sharpe	Research Psychologist	BPVL, ARC, NIDA
Others: N. Goodman	Pharmacologist	BPVL, ARC, NIDA
J.H. Jaffe	Acting Chief	BPVL, ARC, NIDA
L.L. Porrino	Research Psychologist	UBI, CNB, NINDS
COOPERATING UNITS (if any)		
Biology and Psychology of Vulnerability Laboratories		
LAB/BRANCH		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 1.90	PROFESSIONAL: 1.40	OTHER: 0.50
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
<p>Intravenous self-administration (IVSA) is a paradigm that has been used frequently to assess the reinforcing properties of drugs in several animal species. The purpose of this study was to investigate the neuroanatomical and neurochemical bases of IVSA of several psychomotor stimulants. It was found that amfonelic acid, a non-amphetamine type of psychomotor stimulant, was self-administered at doses 9.4 times lower than those at which cocaine was administered. These data suggest that amfonelic acid can act as a reinforcer in rats, and thus, that amfonelic acid may have abuse potential in humans.</p> <p>In addition, studies are underway investigating whether calcium channel blockers may reduce the reinforcing effects of cocaine self-administration in rats. Prior to a test session, several calcium channel blockers were administered to rats whose responding was maintained by cocaine on an FR 10 schedule of reinforcement. Preliminary data suggest that pretreatment with several doses of nifedipine (0.1 to 4.0 mg/kg) may increase the number of cocaine self-injections. Nifedipine may reduce calcium-dependent release of dopamine caused by cocaine. Verapamil and diltiazem had no effect on i.v. cocaine self-administration.</p>		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00111-01 BPVL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurochemical Mechanisms Controlling the Morphine Abstinence Syndrome

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L.G. Sharpe Research Psychologist BPVL, ARC, NIDA

Others: J.H. Jaffe Acting Chief BPVL, ARC, NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biology and Psychology of Vulnerability Laboratories

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.20

PROFESSIONAL:

0.20

OTHER:

0.00

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Since morphine inhibits and naloxone increases their release in the morphine-dependent rat, the neurokinins (substance P, neurokinin A and B, physalaemin, among others) have been postulated to play an important role in the opiate abstinence syndrome. The purpose of this study is to investigate this possibility by administering, to morphine-dependent rats (prior to administration of naloxone), drugs that would be expected to either increase or decrease the efficacy of endogenous neurokinins. A completed study found that captopril (0.3 mg/kg, i.p.), a drug that increases peripheral levels of substance P, enhances the secretory signs of abstinence in the morphine-dependent rat. Moreover, pretreatment with capsaicin (125 mg/kg) prevented the enhanced withdrawal signs associated with captopril administration. It is hoped that this animal model will contribute to the development of drugs that could aid in the clinical management of opiate detoxification.

**Neurochemical Mechanisms Controlling the Morphine Abstinence Syndrome**

In addition, another study has been completed in which the effects of ibogaine were investigated on the morphine abstinence syndrome. Ibogaine, an alkaloid of Tabernanthe iboga H.BN., reportedly interacts with several receptor systems. A patent application for the use of ibogaine in interrupting abuse syndromes in humans has been filed. This particular study did not demonstrate that ibogaine, in non-tremorgenic doses (5 and 10 mg/kg), had a measurable effect on naloxone-precipitated withdrawal in morphine-dependent rats.

**Abstract**

Sharpe, L.G. and Jaffe, J.H.: Modification of naloxone-precipitated withdrawal signs by captopril and capsaicin in the morphine-dependent rat. 17th Annual Meeting, Society for Neuroscience, New Orleans, LA, November 1987.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00112-01 BPVL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effects of Cocaine on Hormone Secretion from the Anterior Pituitary Gland

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	N.S. Pilotte	Staff Fellow	NEI, ARC, NIDA
Others:	E.M. Dax	Chief	NEI, ARC, NIDA
	L.G. Sharpe	Psychologist	BPVL, ARC, NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biology and Psychology of Vulnerability Laboratories

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Cocaine-induced sensitization is thought to be related to long-term changes in the release of dopamine. Since the release of prolactin from the anterior pituitary gland is tonically inhibited by hypothalamic dopamine, the purposes of this study were to compare the effects of single and multiple injections of cocaine on the release of prolactin in chronically catheterized male rats and to assess whether changes in prolactin levels may be used as markers for both dopaminergic function and sensitization of dopaminergic neurons in the central nervous system.

In a recently completed study, the concentration of prolactin in plasma was not found to be affected by single i.v. injections of 1, 3, or 10 mg/kg of cocaine. However, in rats that received programmed infusions of 1 mg/kg of cocaine every 12 minutes for 2 hours over a 10-day period, the pre-infusion concentrations of prolactin were found to be increased in a time-dependent manner, whereas post-infusion levels of prolactin were uniformly decreased by cocaine. Single injections of cocaine increased adrenocorticotrophic hormone (ACTH) in a dose-dependent manner, whereas repeated infusions did not. Thus, it appears that the repeated injections of cocaine do not result in stress, but may involve mechanisms which produce long-term changes in either the tuberoinfundibular dopamine neurons, or the dopamine receptors in the anterior pituitary, or both.

Z01 DA00112-01 BPVL (Cont'd)

**Effects of Cocaine on Hormone Secretion from the Anterior Pituitary Gland**

In progress is research to determine if the brains of rats treated repeatedly with cocaine exhibit differences in receptor binding to dopamine-2 (D2) and serotonin (5-hydroxytryptamine, 5-HT) antagonists, as well as mazindol, neurotensin, and corticotropin-releasing hormone (CRH). The overall purpose is to relate these binding characteristics to chronic cocaine exposure and to cocaine withdrawal in hopes of identifying changes in receptor numbers that may help explain short- and long-term effects of cocaine.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00113-01 BPVL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Self-Administration of Drugs in Aerosol Form by Rats

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	L.G. Sharpe	Research Psychologist	BPVL, ARC, NIDA
Others:	J.H. Jaffe	Acting Chief	BPVL, ARC, NIDA
	L.L. Weinhold	Staff Fellow	BPVL, ARC, NIDA
	A.B. Jaffe	Summer Student	BPVL, ARC, NIDA

## COOPERATING UNITS (if any)

None

## LAB/BRANCH

Biology and Psychology of Vulnerability Laboratories

## SECTION

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.80

## PROFESSIONAL:

1.30

## OTHER:

0.50

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Most drugs that are reinforcing in humans are administered by pulmonary or intranasal routes (e.g., opiates, hallucinogens, cocaine, phencyclidine [PCP], nicotine, cannabis). Indeed, these have become the routes of choice for many compounds because of the immediate reinforcing effects associated with them. Conversely, these routes are used to avoid intravenous administration which is often associated with those at risk for AIDS. Thus, the goal of this study is to develop an animal model for the self-administration of inhaled drugs to make it possible to explore the importance and possible advantages of this paradigm of drug-seeking behavior.

To accomplish this goal, an ultrasonic nebulizer was used to create a drug vapor. Rats were then trained to either lever press or nose poke on a FR 5 schedule of reinforcement for 2 to 5 seconds of drug vapor. A study completed using this paradigm showed that, when given access to sufentanil vapor, rats would press a lever for this opioid in a dose-dependent manner (10 to 75 mg/ml). Further, it was found that naloxone antagonizes this behavior. Moreover, substituting water vapor for all concentrations of sufentanil studied was found to reduce responding to a statistically significant extent within 5 to 20 2-hour sessions.

**The Self-Administration of Drugs in Aerosol Form by Rats**

In addition, related studies showed that it was difficult to maintain responding to amphetamine vapor. One possible explanation for this is that some drug vapors presented in high concentrations may become aversive if they irritate the nasal mucosa and respiratory tract. Further, preliminary evidence has been developed suggesting that rats treated with capsaicin (125 mg/kg, known to deplete substance P) maintain responding to amphetamine better than nontreated rats, perhaps because capsaicin treatment renders the animal less sensitive to the irritating effects of the vaporized drug.

In progress is a study whose goal is to investigate whether rats reared in isolation will self-administer sufentanil vapor in a manner different from rats reared with other rats. An aim is to examine whether patterns of drug-taking behavior are related to dominance behavior quantified from videotapes of social pairings before, and after, the drug sessions.

**Abstract**

Sharpe, L.G., Jaffe, J.H., and Jaffe, A.B.: Rats rapidly learn to self-administer sufentanil in aerosol form. 50th Annual Meeting, Committee on Problems of Drug Dependence, North Falmouth, MA, June 1988.



Neuroendocrinology and Immunology Laboratory — Elizabeth M. Dax, M.D.,  
Ph.D., Chief

## Introduction

The Neuroendocrinology and Immunology (NEI) Laboratory investigates mechanisms by which drugs of abuse, particularly cocaine, act at the sites at which neural, endocrine and immunological factors interact. One specific focus is on the neuroendocrine hormones (i.e., prolactin [PRL], growth hormone [GH], adrenocorticotrophic hormone [ACTH], thyroid-stimulating hormone [TSH], and leutinizing hormone [LH]) which are regulated by neurotransmitters and releasing factors released from the hypothalamus. The principal neurotransmitters involved are dopamine [DA], serotonin [5-hydroxytryptamine, 5-HT], and norepinephrine [NE], each of which may be perturbed by specific drugs. Other regulators include peptide-releasing factors, feedback loops, steroid hormones, and influences from higher central nervous system (CNS) centers, such as mood states. Thus, manipulation of these perturbators or regulators and subsequent measurement of the release of neurohormones may be used to dissect out mechanisms which underlie the effects of drugs on the hypothalamo-pituitary-adrenal (HPA) axis. By examining patterns of secretion and secretion responses to specific manipulations induced by peptide regulators or drugs with known actions on neurotransmitters, the actions of drugs of abuse and the possible mechanisms which underlie these effects, the altered physiology associated with these actions, and possibly mechanisms which may be involved in the addictive process, may be investigated. In addition, hormones interact with the immune system. Thus, studies of alterations in endocrine function may help to explain the altered immune function observed in drug abusers. Moreover, such studies might elucidate the factors which may influence the differences in the progression to acquired immunodeficiency syndrome (AIDS) and to death seen in drug abusers with human immunodeficiency virus (HIV) versus that seen in other groups of HIV-infected individuals.

## Overview

With this as background, the NEI Laboratory conducts studies on the ability of drugs of abuse to perturb CNS function using neurohormonal secretion as a model system. This Laboratory's initial efforts have focused on the mechanisms by which cocaine disrupts dopamine-mediated secretion of hormones. Thus, studies are being conducted to examine hormones with known circadian periodicities in men withdrawing from cocaine. The results indicate that dopaminergically-controlled hormonal secretion is altered. These human studies are also supported by investigations into the mechanisms of these alterations in rats. In addition to this approach, studies are underway to monitor the secretion of neurohormones in response to different regimens of cocaine administration. In subsequent work, receptor and neurotransmitter content of the CNS may be measured after different schedules

of cocaine exposure. To examine the secretion of neurotransmitters and hormones from hypothalami and pituitaries without the influence of higher centers, preparations of these anatomical units are superfused alone and in tandem, with hormones and neurotransmitters being measured in the superfusates. Secretion from dispersed anterior pituitary cells also is being examined. Thus, throughout the studies planned, special efforts are made to dissect out the specific CNS levels at which these drugs act to influence dopaminergically-controlled neurosecretory systems during exposure to different schedules of drug administration.

The special expertise the NEI Laboratory has for conducting and developing radioimmunoassays for hormones and drugs has significantly enhanced the capabilities of the Biology and Psychology of Vulnerability Laboratories. Thus, it is now possible to conduct both epidemiological studies on the incidence of certain neuroendocrine disorders in populations of drug-abusing individuals as well as more basic studies designed to identify neuroendocrine mechanisms which may be involved in the onset and perpetuation of drug abuse, such as the role of neuroendocrine stress responses.

Along these lines, drug abusers constitute a large proportion of those people who have been exposed to the HIV, or who have contracted the disease of AIDS. Thus, it is this group of those infected with HIV who may be expected to be largely responsible for the spread of the virus into the heterosexual community. Moreover, since drugs of abuse are known to perturb immune function, they may be important co-factors in the development of AIDS in those exposed to HIV.

In this regard, the Section of Neuroendocrinology and Immunology evolved from the "AIDS Laboratory" which was established to investigate the prevalence of HIV in drug abusers and the effects of drugs of abuse on the immune system. The AIDS Laboratory formed part of NIDA's effort to curb AIDS in the drug-abusing community by carrying out the laboratory component of a multi-city survey of HIV antibody prevalence in known addicts.

In addition, the NEI Laboratory has carried out a multidisciplinary study of the effects of inhaled nitrites on immune function of lymphocytes. These studies have been carried out in collaboration with the Immunology Section of the Gerontology Research Center (Dr. William Adler, Chief). Inhaled nitrites are abused primarily by homosexual men and it is these men who are the only group of AIDS sufferers with a high prevalence of Kaposi's sarcoma. Thus, it is suspected that nitrites may be responsible for a disturbance in immune function that facilitates the development of this disease. In this regard, a recent study in volunteer subjects at the ARC have shown immune function to be depressed in response to the administration of amyl nitrite. A study on the effects of delta-9-tetrahydrocannabinoid (THC) on the immune function of volunteers has begun; future studies will assess immune function in individuals who are using drugs in combination, a frequent practice. Further, the possible role of hormones in the interactions observed between drugs of abuse and altered immune function are being conducted.



In addition to its research activities, the NEI Laboratory is responsible for carrying out tests to establish the sero-status of individuals at risk for exposure to HIV. The Laboratory is supporting the NIDA national study of sero-prevalence in drug abusers. Studies originating at the ARC have been completed and further studies examining the HIV status of high-risk individuals are in progress.

Another more recent research thrust of the NEI Laboratory is more developmental in nature than the screening approaches and involves raising monoclonal antibodies against new treatment drugs and drugs of abuse that do not hold immediate commercial value. This new section of the NEI Laboratory was created over the last year.

A related but more practically oriented activity of the NEI Laboratory involves carrying out the urine toxicology services for the ARC. This has given the Laboratory the capability of adapting drug assays for measurement of drug levels in plasma and tissue samples as well as urine.

**More specifically, the Goals of the NEI Laboratory are:**

- a) To investigate the disturbances of neuroendocrine secretion caused by drugs of abuse, in order to investigate their mechanisms of action, the altered physiological consequences of their abuse, and possibly the mechanisms which contribute to perpetuation of a drug habit.
- b) To continue research into basic mechanisms of neuroendocrine secretion.
- c) To investigate the possible interactions between drugs of abuse and neurohormones and their relationship to altered immune function. Further, the hypothesis that drugs of abuse as immunodepressors may be co-factors in the development of AIDS in HIV-infected people will be tested.
- d) To determine the HIV antibody status of ARC volunteers, research subjects and addicts in the NIDA HIV-antibody prevalence study.
- e) To provide measurements of drug concentrations in body fluids and tissue extracts.

#### **Summary of Ongoing Research**

##### **A. Changes in Neurosecretion Caused by Drugs of Abuse**

The purpose of these investigations is to define neuroendocrine changes in response to administration of drugs in order to determine the mechanisms of their action, the physiological consequences of taking abused drugs and possibly to investigate mechanisms of addiction.

Cocaine may act primarily on synaptic sites inhibiting the uptake of dopamine, and, at the same time, directly stimulating dopamine release. Supporting this contention, in chronic administration paradigms, cocaine causes dopamine depletion. It may have similar effects on serotonergic systems. Neuroendocrine secretion in men acutely withdrawn from cocaine is being followed (Project number Z01 DA00007-02 NEI). By measuring prolactin and cortisol at 2 hour intervals over 24 hours up to the 21st day after cocaine cessation, it has been shown that the dopamine controlled hormone, prolactin, is higher in those men than in non-cocaine abusers. Cortisol levels (controlled by ACTH and by input from serotonergic mechanisms) were not different from controls. Further, the diurnal variation of prolactin secretion was not present up to 21 days after cocaine cessation. The results suggest that the neuroendocrine effects of cocaine may persist for at least 21 days after withdrawal.

In the next series of studies, men withdrawing from cocaine will have provocative endocrine tests to establish whether those men have hypersensitivity to neurosecretory regulators at the level of the anterior pituitary cells. Subsequently, studies are being designed to examine the sensitivity of the hypothalamus to drugs which perturb the neurotransmitters, dopamine and serotonin.

The human studies are being followed up by studies in rats in order to further explore mechanisms (Project number Z01 DA00008-02 NEI). The neuroendocrinology of administering cocaine in different regimens is being examined in an effort to investigate the progression of changes that occurs as cocaine is administered in increasing amounts and to investigate whether some of these changes resolve when cocaine is withdrawn. Neurotransmitter content and receptor parameters will be quantified. Further, a regimen that parallels the endocrine changes seen in humans will be sought to define the most appropriate model. In the same rats, cardiac manifestations of this regime will be investigated, since cardiac complications of cocaine are the cause of acute deaths in cocaine users.

Since there are many influences on the hypothalamus of the intact brain, rat studies in which hypothalami, anterior pituitary gland or hypothalami and pituitaries in tandem are perfused, will examine direct effects of cocaine (and other drugs) on the hypothalamus or anterior pituitary. This will be evaluated in tissues naive to the drugs and those from rats which have been exposed in vivo. Again, neurohormones will be measured as will the release of neurotransmitters. Using reverse hemolytic plaque assays, secretion from single anterior pituitary cells may be assessed (Project number Z01 DA00008-02 NEI). Cocaine does not seem to have any direct effect on prolactin secretion in anterior pituitary cells. Thus, the possibility of an effect on secretion of releasing



factors from hypothalamic cells will be investigated using the same basic experimental approach. To examine release of neurotransmitters in rats in vivo, microdialysis techniques are being established in the Laboratory.

Alterations in neuroendocrine secretion have also been examined in men taking delta-9-tetrahydrocannabinol (THC) (Project number Z01 DA00006-02 NEI). This molecule has steroid-like properties which are likely to modify neuroendocrine hormone secretion since steroids are important regulators of the endocrine system. It is hoped that these studies will reveal some important information on endocrine-immune system interrelationships. Some of these investigations will be extended in rats to further clarify possible mechanisms underlying the activity of THC. For example, receptor mechanisms will be assessed. Particular attention will be paid to the possible role of THC in altering regulation of endocrine systems.

It has been established that in ARC volunteers, divided into groups according to aggression and impulsivity scales, endocrine responses to a challenge by a drug with predominantly serotonergic effects are attenuated in the more aggressive/impulsive men (Project number Z01 DA00013-01 NEI). These studies are being extended by examining responses to a more specific serotonergic drug, meta-chlorophenylpiperazine (mCPP). Administration of the serotonergic drug in more chronic regimes to examine the treatment effects on aggressive/impulsive behavior is planned, as well as concomitant measurements of neuroendocrine parameters in an effort to clarify mechanisms which may subserve the drug's actions.

#### **B. Mechanisms of Neuroendocrine Secretion**

The above-mentioned studies were designed to hold potential for elucidating mechanisms of neurosecretion. Findings that are being explored further are the role of individual hypothalamic neurotransmitters in mediating diurnal rhythms. In the men withdrawing from cocaine there was a disruption of the prolactin diurnal rhythm (Project number Z01 DA00007-02 NEI), while cortisol diurnal rhythms remained intact. ACTH rhythms in these men have subsequently been examined.

Hormones and neurotransmitters are sequestered in two or more intracellular pools. However, the significance of these pools in cell function is unknown (Project number Z01 DA00009-02 NEI). In order to examine release from the intracellular pools, investigations using direct visualization of the secretion of prolactin from single anterior pituitary cells by use of the reverse hemolytic plaque assay (RHPA) will be carried out. Other experiments will examine secretion of newly synthesized hormone by combining the RHPA with autoradiographic techniques.

### C. Neuroendocrine-Immune System Interactions

There is extensive evidence that drugs of abuse induce changes in immune function. Few studies have been carried out where the drug administration and the immune function of lymphocytes have been temporally related. A study of immune function of lymphocytes of men taking volatile nitrites (the use of which has been linked with the development of Kaposi's sarcoma in AIDS), has been carried out. During the period when the volunteers were exposed to amyl nitrite, immune function changes occurred. Depressed natural killer cell activity and T-lymphocyte cell function were observed (Project number Z01 DA00004-02 NEI). A similar protocol studying the effects of delta-9-THC on lymphocyte function is in progress (Project number Z01 DA00006-02 NEI). However, the THC study also includes detailed endocrinological studies, in order to examine any temporal relationships between the alterations in neuroendocrine and immune function.

The hypothesis that drugs of abuse may be co-factors in the development of AIDS in HIV infected people is being tested. Blood samples from men with documented drug histories, medical histories and HIV status are being collected. The relationship between HIV status and clinical status in relationship to drug histories will be correlated.

### D. HIV - Status of Risk Groups

The HIV Serology Laboratory processes approximately 200 samples per week. A major portion of these samples are supporting the multicity survey being conducted by NIDA, in which the HIV status in drug abusers is being determined. The origin of the HIV virus in its present form of efficacy and ability to produce the autoimmune deficiency syndrome is unknown. Several thousand plasmas from missionaries traveling between Africa and the U.S. between 1968 and 1983 have been examined. Although this group of people is not high risk, it is a group with high casual contact with the African people in whom the virus is endemic. Selected plasmas are being examined for the presence of related retrovirus (Project number Z01 DA00012-01 NEI).

None of these plasmas were found to be positive for HIV antibodies by Western Blot despite about 200 being ELISA positive. The ELISA positive samples and twice the number of as closely matched controls as possible will be further screened. In 1129 plasmas from people admitted to Lexington, KY, between 1971 and 1972, 29 were found to be ELISA positive (Project number Z01 DA00002-03 NEI, in 1987 ARC Annual Report). However, followup revealed no excess mortality compared with matched controls among the seronegative group. It is of interest that unexpectedly high proportions of these groups were ELISA positive.

## E. Measurements of Drugs and Their Metabolites in Body Fluids and Tissues

The urine toxicology radioimmunoassays are being adopted to quantify drug concentrations in other body fluids in addition to urine, and in tissue extracts. The ability to quantify drugs in tissues will be of value when drug effects are being determined because tissue and plasma concentrations as well as doses may be related to responses.

## Publications

Dax, E.M. and Contoreggi, C.S.: HIV transmission, lab technicians, and open-toed shoes. JAMA 259: 687, 1988. (Letter).

Dax, E.M., Reichman, C., Fullerton, M., Wallace, C., Smith, A.I. and Funder, J.W.: B-Endorphin and dynorphin levels in pituitary and hypothalamus of aging rats. Neuroendocrinology 47: 241-248, 1988.

Dax, E.M. and Sugden, D.: Age associated changes in pineal adrenergic receptors and melatonin synthesizing enzymes in the Wistar rat. J. Neurochem. 50: 468-472, 1988.

Lange, W.R., Cone, E.J. and Jaffe, J.H.: Study of Haitian boat people shows prevalence of HBV and HIV markers. Public Health Reports 103: 98-99, 1988.

Lange, W.R. and Dax, E.M.: Human immunodeficiency virus infection and international travel. American Family Physician 36: 197-208, 1987.

Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M. and Jaffe, J.H.: Nitrite inhalants: Patterns of abuse in Baltimore and Washington, D.C.. Am. J. Alcohol and Drug Abuse 14: 29-40, 1988.

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A. and Jaffe, J.H.: HIV infection in Baltimore: Antibody seroprevalence rates among parenteral drug abusers and prostitutes. MD Medical J. 36: 757-761, 1987.

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A. and Jaffe, J.H.: The ARC Epidemiology Collaborating Group: Geographic distribution of human immunodeficiency virus markers in parenteral drug abusers. Am. J. Pub. Health 78: 443-446, 1988.



## Invited Publications or Chapters

Dax, E.M.: Age-related Changes in Membrane Receptor Interactions. In Sactor, B. (Ed.): Endocrine and Metabolism Clinics of North America: Endocrinology and Aging. W.B. Saunders Company, 1988, Vol. 16, pp. 947-963.

Dax, E.M.: Normal Aging. In Warne, R.W. and Prinsley, D.M. (Eds.): A Manual of Geriatric Practice, 1988, pp. 2-13.

Dax, E.M., Adler, W.H., Nagel, J.E., Lange, W.R. and Jaffe, J.H.: Effects of Nitrites on the Immune System of Humans.. In Haverkos, H.W. and Dougherty, J.A. (Eds.): NIDA Research Monograph #83, 1988, pp. 86-95.

Lange, W.R., Dax, E.M., Haertzen, C.A., Snyder, F.R. and Jaffe, J.H.: Nitrite Inhalants, Contemporary Patterns of Abuse. In Haverkos, H.W. and Dougherty, J.A. (Eds.): NIDA Research Monograph #83, 1988, pp. 86-95.

Lange, W.R., Kreider, S.D. and Dax, E.M.: Counseling the HIV antibody positive traveler relative to immunization protection and malaria prophylaxis. Proceedings of Conference on International Travel Medicine, Zurich, Switzerland, April 1988.

## Abstracts

Dax, E.M., Adler, W.H., Nagel, J.E., Lange, W.R. and Jaffe, J.H.: Immunosuppression persists during chronic volatile nitrite exposure. Proceedings of the IVth International Conference on AIDS, Stockholm, Sweden, 1988. Abstract #2050.

Dax, E.M., McNair, C.L., Partilla, J.S., Hymer, T.K., Kohn, S.R., Gregerman, R.I. and Katz, M.S.: Food restriction modulates age-related changes in beta-adrenergic stimulated glycogenolysis in hepatocytes of Fischer 344 rats. Proceedings Gerontological Society of America, 1988.

Dax, E.M., Weddington, W.W., Pilotte, N.S. and Jaffe, J.H.: Release of prolactin and cortisol following cocaine cessation in men. Proceedings 19th Annual Meeting, Society for Neuroscience, Toronto, Canada, 1988. Abstract #422.8.

Deshpande, S.B., Pilotte, N.S. and Warnick, J.E.: Electrophysiological evidence for a sex difference in the potentiating effect of thyrotropin-releasing hormone (TRH) on the spinal reflex in neonatal rats. Symposium on Recent Advances in the Biomedical Significance of Thyrotrophin-releasing Hormone (TRH). NY Acad. Sci., November 9-11, 1987.



## Abstracts (Cont'd)

Pilotte, N.S. and Burt, D.R.: Adenohypophyseal TRH receptors and release of prolactin (PRL) increase after neonatal treatment with monosodium glutamate. Proceedings of Endocrine Society Annual Meetings, New Orleans, 1988. Abstract #186.

Pilotte, N.S. and Sharpe, L.G.: Chronic cocaine alters the release of prolactin in male rats. Proceedings 18th Annual Meeting, Society for Neuroscience, Toronto, Canada, 1988. Abstract #33.11.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00004-03 NEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Inhalable Nitrites - Immune Function and Abuse Potential		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.M. Dax	Chief NEI, ARC, NIDA
Others:	J.H. Jaffe	Acting Chief BPVL, ARC, NIDA
	W.R. Lange	Medical Director NEI, ARC, NIDA
	R.I. Herning	Chief CHP, ARC, NIDA
	R.M. Litow	Research Technologist NEI, ARC, NIDA
	N. Robinson	Registered Nurse NEI, ARC, NIDA
COOPERATING UNITS (if any)  Dr. William H. Adler and Dr. James A. Nagel (Clinical Immunology Section, Gerontology Research Center, NIA)		
LAB/BRANCH Neuroendocrinology and Immunology Laboratory		
SECTION Clinical Biology Branch		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	0.25	0.75
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>             The intake and frequency of inhalation of volatile nitrites has been associated with the incidence of Kaposi's sarcoma in people suffering from AIDS. Animal and <u>in vitro</u> lymphocyte studies have shown that immune cell function can be altered by these agents. However, no study has related directly the effects of nitrites administered <u>in vivo</u> to disturbances of immune function in humans. Thus, a study has been conducted in healthy, HIV-negative volunteers examining this possible relationship. An inhalation protocol in which the subject inhaled 3 doses of amyl nitrite for 3 days and 1 dose on the fourth day has been conducted. In an extended protocol, a second group of volunteers was administered subsequent, single inhalations of nitrite 3-4 days apart, to a total of 13 inhalations over 3 weeks. Lymphocytes were then harvested and used to conduct a battery of immune function tests on 2 occasions prior to the inhalation protocol, immediately following the last dose, and at 1, 4, and 7 days after the last dose. Results showed a decrease in natural killer cell activity, the lymphocyte function reputedly responsible for tumor cell scavenging. Notably, single doses of nitrite administered at 3-4 day intervals continued to suppress this activity. Lymphocyte numbers and subsets were not altered during the inhalation protocols, but showed a non-specific rise on cessation of the drug.           </p>		

## Inhalable Nitrites - Immune Function and Abuse Potential

Moreover, discrepancies between mitogen stimulated [<sup>3</sup>H]-thymidine incorporation, a measure of the activity potential of lymphocytes, and antibody production by the T lymphocyte-dependent B-cells, indicated a deficit in T-cell function during nitrite exposure.

Parenthetically, the nitrites were demonstrated to have minimal abuse potential.

## Publications

Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M. and Jaffe, J.H.: Nitrite inhalants: Patterns of abuse in Baltimore and Washington, D.C. Am. J. Alcohol and Drug Abuse 14: 29-40, 1988.

Dax, E.M., Adler, W.H., Hagel, J.E., Lange, W.R. and Jaffe, J.H.: Effects of Nitrites on the Immune System of Humans. In Haverkos, H.W. and Dougherty, J.A. (Eds.): NIDA Research Monograph #83, 1988, pp. 86-95.

Lange, W.R., Dax, E.M., Haertzen, C.A., Snyder, F.R. and Jaffe, J.H.: Nitrite Inhalants, Contemporary Patterns of Abuse. In Haverkos, H.W. and Dougherty, J.A. (Eds.): NIDA Research Monograph #83, 1988, pp. 86-95.

Dax, E.M., Adler, W.H., Nagel, J.E., Lange, W.R. and Jaffe, J.H.: Immunosuppression persists during chronic volatile nitrite exposure. Proceedings of the IVth International Conference of AIDS, Stockholm, Sweden, 1988. Abstract #2050.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA00005-02 NEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) HIV Prevalence: In Depth Survey of Baltimore		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: E.M. Dax  Others: W.R. Lange J.H. Jaffe	Chief  Medical Director Acting Chief	NEI, ARC, NIDA  NEI, ARC, NIDA BPVL, ARC, NIDA
COOPERATING UNITS (if any)  None		
LAB/BRANCH Neuroendocrinology and Immunology Laboratory		
SECTION Clinical Biology Branch		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.50	PROFESSIONAL: 0.25	OTHER: 0.25
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>The seroprevalence of HIV antibodies in surveyed intravenous drug users (IVDUs) who were either recently enrolled into treatment, or were on a waiting list for enrollment, was 29%. The rate among ARC research subjects with parenteral drug use histories has averaged 24%, and among area prostitutes with heavy drug use histories, 34%. In Baltimore, 94% of IVDUs had shared needles and, even though HIV seropositivity was not associated with a needle-sharing history, there was an association between the intensity of sharing and the probability of being seropositive. A much stronger association was observed between seropositivity and "shooting gallery" visitation, suggesting that this milieu of sharing, rather than other environments, is the real risk factor.</p> <p>Very distinct ethnic group differences were observed with respect to rates of HIV infection, with Blacks being much more likely to be seropositive than Whites (odds ratio = 8.18, 95% CI 3.35-19.97). There was no significant difference in HIV infection between Blacks in Baltimore and in New York City.</p>		



**HIV Prevalence: In Depth Survey of Baltimore**

Shooting gallery visitation appears to be much more of a phenomenon among Black IVDUs than it is in White IVDUs ( $\chi^2 = 8.23$ ,  $p < 0.01$ ). HIV infection has appreciably penetrated Baltimore's addict community. The overall seroprevalence rate in Baltimore in 1986 (29%) approximated that of New York in 1979 (27%), where the rate subsequently jumped to 58% in some areas by 1984, and has increased to 60% in 1987.

Hepatitis antigen and antibody status of these subjects has also been assessed. There was found to be no demonstrable concordance of hepatitis B infection and HIV infection. Other data concerning hepatitis are being analyzed.

**Publications**

Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M. and Jaffe, J.H.: Nitrite inhalants: Patterns of abuse in Baltimore and Washington, D.C. Am. J. Alcohol and Drug Abuse 14: 29-40, 1988.

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A. and Jaffe, J.H.: HIV infection in Baltimore: antibody seroprevalence rates among parenteral drug abusers and prostitutes. MD Medical J. 36: 757-761, 1987.

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A. and Jaffe, J.H.: The ARC Epidemiology Collaborating Group: Geographic distribution of human immunodeficiency virus markers in parenteral drug abusers. Am. J. Pub. Health 78: 443-446, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA00006-02 NEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Cannabinoids and Their Effects on the Immune System and Cognitive Function</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.M. Dax	Chief NEI, ARC, NIDA
Others:	J.H. Jaffe	Acting Chief BPVL, ARC, NIDA
	W.R. Lange	Medical Director NEI, ARC, NIDA
	R.M. Litow	Research Technologist NEI, ARC, NIDA
	N. Robinson	Registered Nurse NEI, ARC, NIDA
COOPERATING UNITS (if any)  Clinical Immunology Section, GRC, NIA (Drs. William Adler and James A. Nagel)		
LAB/BRANCH Neuroendocrinology and Immunology Laboratory		
SECTION Clinical Biology Branch		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	0.25	0.75
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Delta-9-tetrahydrocannabinol (THC) has been hypothesized to influence immune function. However, this has not been investigated in a comprehensive fashion in humans. Hence, the purpose of this study is to measure and study the effects of THC on immune function. To investigate immune-endocrine correlations, hormone parameters defining the activity of the hypothalamo-pituitary-adrenal axis will be measured during THC administration. The effects of THC on cognitive function will also be investigated. Experienced substance abusers, who are heavy users of THC, will be recruited. Immune function of lymphocytes <u>in vitro</u> will be investigated during orally administered THC and during a washout phase.</p> <p>Since THC is often used with nitrites (see Project # Z01 DA0004-02 NEI), the effect of THC administration together with nitrites will be examined in a subsequent study.</p>		

Z01 DA00006-02 NEI

**Cannabinoids and Their Effects on the Immune System and Cognitive Function  
Publication**

Dax, E.M., Weddington, W.W., Pilotte, N.S. and Jaffe, J.H. Release of prolactin and cortisol following cocaine cessation in men. Proceedings 18th Annual Meeting, Society for Neuroscience, Toronto, Canada, 1988, Abstract #422.8.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00007-02 NEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Hormonal Diurnal Rhythms During Cocaine Withdrawal		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.M. Dax	Chief NEI, ARC, NIDA
Others:	J.H. Jaffe N.S. Pilotte W.W. Weddington	Acting Chief Staff Fellow Visiting Scientist BPVL, ARC, NIDA NEI, ARC, NIDA TEI, ARC, NIDA
COOPERATING UNITS (if any) None		
LAB/BRANCH Neuroendocrinology and Immunology Laboratory		
SECTION Clinical Biology Branch		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 2.00	PROFESSIONAL: 1.00	OTHER: 1.00
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>Cocaine withdrawal (and withdrawal from other drugs) is associated with sleep disturbances. Whether the sleep disturbances (in a situation similar to jet lag) are related to the lifestyle of cocaine abusers, or diurnal rhythms are disturbed secondary to CNS neurotransmitter alterations, has not been determined. In men known to be cocaine abusers, the diurnal rhythms of hormones have been examined during cocaine withdrawal. Prolactin secretion is under tonic inhibition by dopamine from the hypothalamus. Cortisol release is mainly mediated through serotonergic mechanisms. In the volunteers withdrawn from cocaine, prolactin levels were higher than in men who had not taken cocaine, and prolactin diurnal rhythms were not present. The men were followed for up to 21 days with little change in the profiles of prolactin release. Cortisol levels and rhythms were found to be similar to controls over this withdrawal period. These results suggest that chronic cocaine abuse results in dysfunction of dopamine-controlled mechanisms of neurosecretion.</p>		



**Hormonal Diurnal Rhythms During Cocaine Withdrawal**

The alterations in the hypothalamo-pituitary-adrenal axis resulting from chronic cocaine abuse will be further defined. This study will be conducted in volunteers whose serotonergic and dopaminergic functions are predictably manipulated by tests that perturb the hypothalamic-pituitary-adrenal axis at a known level. Standard endocrine diagnostic tests (TRH, CRF stimulation and L-DOPA suppression) in conjunction with administration of drugs that perturb dopaminergic and serotonergic function will be used.

It is hoped that this study will provide further information on dopaminergic control of hormonal secretion and its role in maintaining diurnal rhythms of hormones and that it may provide an important means for assessing the efficacy of treatment protocols.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00008-02 NEI
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) The Effects of Cocaine on Hormone Secretion from the Anterior Pituitary
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: E.M. Dax N.S. Pilotte	Chief Staff Fellow	NEI, ARC, NIDA NEI, ARC, NIDA
Others: L.G. Sharpe J. Partilla C. Contoreggi	Research Psychologist Research Chemist Staff Fellow	BPVL, ARC, NIDA NEI, ARC, NIDA NEI, ARC, NIDA

COOPERATING UNITS (if any)  None
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LAB/BRANCH Neuroendocrinology and Immunology Laboratory
--

SECTION Clinical Biology Branch
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
--

TOTAL MAN-YEARS: 2.00	PROFESSIONAL: 1.00	OTHER: 1.00
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CHECK APPROPRIATE BOX(ES).		
<input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews	<input type="checkbox"/> (b) Human tissues	<input checked="" type="checkbox"/> (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
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Tolerance to the physiologic effects of cocaine may occur after as little as a single dose of cocaine. At least part of this effect is considered to be dopamine mediated. Prolactin, an anterior pituitary hormone, is regulated primarily by dopamine which is released from a discrete population of neurons within the medial basal hypothalamus. Thus, prolactin release in the male rat is an indirect measure of dopamine release. Secretion mechanisms will be examined during different cocaine administration regimens, using several techniques now established in this Laboratory. Studies in which pituitary hormones have been measured in the blood of catheterized rats have demonstrated that adrenocorticotrophin (ACTH) is released in response to cocaine administration. Stress hormone release may be altered up to 10 days after cocaine administration in animals which have received as little as a single dose of cocaine. Thus, direct secretion of dopamine will be examined in the hypothalamo-portal blood of live, anesthetized animals, before and after acute cocaine treatment and, subsequently, in rats treated with cocaine for varying periods of time. In isolated pituitaries and hypothalami, perfused alone or in tandem, the output of dopamine and neuropeptides will be examined concomitantly with the release of prolactin in order to examine release which is not under the influence of higher centers.

**The Effects of Cocaine on Hormone Secretion from the Anterior Pituitary**

Neurotransmitter release will be measured by microdialysis, with microdialysis probes being inserted stereotaxically through fixed cannulae which have been previously inserted under anesthesia. In this manner, secretion may be studied in particular brain areas of unanesthetized rats to examine neurosecretion in vivo. In addition, prolactin release will be examined in dispersed anterior pituitary cells to assess cocaine's effects on secretion at the level of anterior pituitary cell.

Thus, this project will assess the role of the dopaminergic system in cocaine tolerance and the use of prolactin as an accurate marker for dopaminergic function in cocaine-treated animals will be assessed.

**Publications**

Pilotte, N.S. and Sharpe, L.G. Chronic cocaine alters the release of prolactin in male rats. Proceedings 18th Annual Meeting, Society for Neuroscience, Toronto, Canada, 1988, Abstract #33.11.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00009-02 NEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Mobilization of Pools of Prolactin as a Function of Drug Environment		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)  PI:        N.S. Pilotte                      Staff Fellow                      NEI, ARC, NIDA		
COOPERATING UNITS (if any)  None		
LAB/BRANCH Neuroendocrinology and Immunology Laboratory		
SECTION Clinical Biology Branch		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 2.00	PROFESSIONAL: 1.00	OTHER: 1.00
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) One physiological consequence of the administration of drugs of abuse such as cocaine, opiates or amphetamine, is increased release of prolactin from the anterior pituitary gland. Prolactin, like other hormones and neurotransmitters, appears to be sequestered in 2 or more intracellular pools. The release of hormone from each pool is governed normally by the actions of releasing or release-inhibiting factors. However, the administration of cocaine, opiates, or amphetamine may alter the secretion of prolactin by a direct action on the lactotrope (prolactin-secreting cell). These agents may modify the ability of the cell to produce and release new hormone, or may affect the release of the older, stored pool. These possibilities will be assessed by visualizing directly the secretion of prolactin from single cells challenged with the drugs in combination with known secretagogues through the use of a reverse hemolytic plaque assay. This technique will be modified to permit the production of radioisotopically-labelled new hormone. Both the secretion and sequestration of the labelled hormone will be monitored by measuring hemolytic plaque formation using autoradiography. It is hoped that these experiments, using the lactotrope as a model system, will permit the identification of the possible mechanism(s) by which drugs of abuse alter the endocrine regulatory systems and provide insight into similar processes which occur in neuronal systems.		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00010-01 NEI
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Development of Monoclonal Antibodies to Drugs and Hormones

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.M. Dax	Chief	NEI, ARC, NIDA
Others: C.Dersh	Chemist	NEI, ARC, NIDA
M.M.S. Lo	Chief, MBG Unit	MPL, ARC, NIDA
R. Zaczek		

COOPERATING UNITS (if any)  
None

LAB/BRANCH  
Neuroendocrinology and Immunology Laboratory

SECTION  
Clinical Biology Branch

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 2.00	PROFESSIONAL: 0.25	OTHER: 1.75
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CHECK APPROPRIATE BOX(ES)

<input type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input checked="" type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Usually antibodies to treatment drugs, drugs of abuse, or hormones are not commercially available unless there is wide market. Moreover, treatment drugs, such as buprenorphine, are unlikely to have antibodies developed until the efficacy of the drug is established. Therefore, this Laboratory is developing antibodies to buprenorphine in order to establish a radioimmunoassay for the compound. Mice immunized with buprenorphine have been found to demonstrate the presence of antibodies on initial tests. Thus, spleen cells will be harvested and fused to myeloma cell which produces cell lines. Testing for production of antibodies in the cell line will then be carried out and any clones producing highly specific and high affinity antibodies will be isolated. Subsequently, buprenorphine antibodies will be used to establish a radioimmunoassay so that the drug may be quantitated in urine, plasma and tissue extracts. Other drugs that antibodies may be raised against include amphetamine and methamphetamine, cocaine and cocaine metabolites, and metachlorophenylpiperazine (mCPP). Antibodies are also presently being raised against vasopressin and rat prolactin, for which commercially available antibodies are limited.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00011-01 NEI
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Neuroendocrine Correlates of HIV Infection and the Development of ARC and AIDS
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: E.M. Dax	Chief	NEI, ARC, NIDA
Others: W.R. Lange	Medical Director	NEI, ARC, NIDA

COOPERATING UNITS (if any) None
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LAB/BRANCH Neuroendocrinology and Immunology Laboratory
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SECTION Clinical Biology Branch
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
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TOTAL MAN-YEARS: 1.00	PROFESSIONAL: 0.50	OTHER: 0.50
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CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
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The human immunodeficiency virus infects the central nervous system, resulting in a wide range of neurological deficits. One problem in the management of HIV-infected people is predicting the disease's prognosis and course. The control of the neuroendocrine system and many feedback loops are a property of the CNS, particularly of the hypothalamus and several studies have shown disruption of neuroendocrine function. Thus, neuroendocrine/endocrine status will be correlated with HIV status, clinical history, drug history, and the presence of opportunistic infections in a large group of drug abusers. To date, clinical data from 800 patients have been collected. HIV antibody status and hormonal measurements are now planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00012-01 NEI
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
HIV Sero-Status in Missionaries from Africa, 1968-1983

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:        W.R. Lange                      Medical Director                      NEI, ARC, NIDA

Others: E.M. Dax                      Chief                      NEI, ARC, NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH  
Neuroendocrinology and Immunology Laboratory

SECTION  
Clinical Biology Branch

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 1.00	PROFESSIONAL: 0.50	OTHER: 0.50
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CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects            ☒ (b) Human tissues            ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The origins and timing of HIV spread into the United States remain in question. One possibility is that alterations in the virus' genetic makeup led to its current pathogenic properties; however, a similar virus may have been transported from Africa, where HIV is endemic. Approximately 6,000 plasma samples from missionaries travelling between Africa and the U.S. have been screened between 1968 and 1983. Although the group may be considered low risk for sexually transmitted diseases, they are a group with a high incidence of casual contact with the African people. Upon ELISA screening of these plasma samples, approximately 200 plasmas were found to be positive; however, none was found to have HIV specific proteins detected by Western blot. Further analyses of the HIV proteins are being conducted. Selected plasma samples are being screened for related virus, including HTLV-1.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00013-01 NEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Neuroendocrine Correlates of Aggressive/Impulsive Behavior		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	Elizabeth M. Dax      Laboratory Chief	NEI, ARC, NIDA
Others:	J.H. Jaffe      Acting Chief	BPVL, ARC, NIDA
	C.S. Contoreggi      Staff Fellow	NEI, ARC, NIDA
	D.H. Fishbein      Staff Fellow	NEI, ARC, NIDA
	N.S. Pilotte      Staff Fellow	NEI, ARC, NIDA
COOPERATING UNITS (if any)  None		
LAB/BRANCH Neuroendocrinology and Immunology Laboratory		
SECTION Clinical Biology Branch		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.0	1.5
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) When men grouped according to their aggressive/impulsive scores on standard psychological tests are challenged with a serotonergic stimulator, such as fenfluramine, the neuroendocrine response is attenuated in the more aggressive, more impulsive men, suggestive of alterations in central serotonergic mechanisms. Further, preliminary studies suggest that hostility ratings decrease with fenfluramine administration, suggesting possible treatment strategies. Aggression and impulsivity may be important personality characteristics in initiating and perpetuating addictive behavior. In order to investigate mechanisms underlying this behavior, to establish neuroendocrine markers, to suggest treatment possibilities, and to assess the efficacy of treatment paradigms, these studies are being extended with the more specific serotonergic agonist, meta-chlorophenylpiperazine (mCPP). Preliminary studies will examine whether mCPP administration gives results similar to fenfluramine. Subsequent studies will examine serotonergic and dopaminergic secretion in greater detail. Using neurohormones as markers of these responses, secretion will be examined in the presence of either a serotonergic or dopaminergic agonist (mCPP or bromocryptine, respectively). Neuroendocrine provocation tests will then be used to further define alterations of function in the aggressive men.		



## **Preclinical Pharmacology Branch**

**Steven R. Goldberg, Ph.D., Chief**

### **Introduction**

The Preclinical Pharmacology Research Branch conducts research on the behavioral effects of drugs functioning as reinforcing, punishing or discriminative stimuli, and into ways to alter established behavior controlled by non-drug events such as food or electric shock. It also studies the role of genetics in determining the effects of drugs of abuse. Studies cover a wide range of topics, including the pharmacology of opioid, psychomotor stimulant and benzodiazepine dependence, alterations in the acquisition and retention of classically conditioned behavioral and physiological responses to drugs of abuse, the consequences of repeated drug administration, and environmental and genetic determinants of drug-seeking and drug-taking behavior. Drugs are also evaluated to characterize physiological and toxic actions which accompany acute and prolonged administration, to delineate the mechanisms responsible for these effects, and to establish methods for preventing or reversing the effects. Research is carried out in both primates and non-primates. New drugs are evaluated for abuse potential by comparing their reinforcing, aversive and discriminative stimulus effects, as well as their effects upon neurophysiologic systems, with the effects of prototypic drugs of abuse.

**Behavioral Pharmacology and Genetics Laboratory - Steven R. Goldberg, Ph. D., Chief**

### **1. Section of Behavioral Pharmacology**

#### **Overview**

The Behavioral Pharmacology Section is responsible for research on the reinforcing effects of drugs of abuse, the influence of such drugs on learned operant behavior controlled by different events, and the discriminative stimulus effects of these drugs. The roles of drugs of abuse from several different pharmacological classes, including psychomotor stimulants, opioids, sedative-hypnotics, and benzodiazepines, are being investigated with respect to how the opportunity for occasional drug self-administration leads to long sequences of integrated behavior culminating in self-administration of the drug, and how administration of these drugs alters ongoing behavior controlled by non-drug events such as food presentation or electric shock delivery.

Behavioral effects of psychomotor stimulants are evaluated to characterize the complex and diverse pharmacology of these compounds and the range of behavioral and toxic actions which accompany their acute or chronic

administration. Different routes of administration are employed in rodent and primate species, recognizing the marked differences in effects that may occur across routes and species.

The positive reinforcing, as well as the punishing, effects of these drugs are being studied to develop an understanding of how drug-seeking behavior becomes strong and persistent, and how it might be weakened by pharmacologic and behavioral means. These objectives are pursued using a variety of experimental procedures, including: (a) assessing the reinforcing effects of these drugs using intravenous self-administration procedures; (b) examining their effects as noxious stimuli using schedules of punishment of ongoing behavior by i.v. drug injections, or schedules of termination or postponement of i.v. drug injections; (c) quantifying their behavioral effects using fixed-interval and fixed-ratio schedules of food, or electric shock delivery or electric-shock postponement, as baselines; and, (d) determining their effects as discriminative stimuli using two-lever choice situations. The use of a host of behavioral performances in these experiments provides a comprehensive picture of the spectrum of effects that can be anticipated in man. Integrated with this work are experiments designed to clarify behavioral, environmental and historical factors which modulate the impact of drug administration.

Collaborative studies are being pursued with other laboratories at the ARC. For example, collaborative studies of neurochemical correlates of the behavioral actions of acutely administered psychomotor stimulants and of chronically administered narcotic antagonists are being pursued with the Neuroscience Branch utilizing studies of receptor binding. Comparative studies of repeated sequences of drug-seeking behavior controlled by i.m. administration of various doses of morphine or placebo under complex second-order schedules in humans and in non-human primates are being pursued jointly with the Biology of Dependence and Abuse Potential Assessment Laboratory.

The long-term goals of the Behavioral Pharmacology Laboratory continue to focus on environmental conditions which determine whether drugs have positive reinforcing or aversive effects on the use of complex second-order schedules of drug injection in humans and non-human primates to investigate the control of drug-seeking behavior by associated environmental stimuli, and on determination of the pharmacological mechanisms of action of the behavioral, physiological and toxic effects of drugs of abuse. Some immediate specific aims are:

To analyze the mechanism underlying the reinforcing actions of cocaine by assessing the effects of a series of cocaine metabolites and analogs both as reinforcers and as modifiers of schedule-controlled behavior, correlating these behavioral effects with biochemical actions.

To investigate reinforcing effects of cocaine and morphine using second-order scheduling procedures that minimize cumulative effects of successive injections and allow a dissociation of reinforcing

effects from other behavioral effects of the drug. These procedures may provide unique baselines for: (a) investigating the role of environmental stimuli previously associated with drug injection in sustaining drug-seeking behavior when drug is no longer available, (b) comparing the reinforcing effects of opioids and drugs acting through non- $\mu$  receptor mechanisms, and (c) cross-validating human and animal models of drug abuse.

To establish the behavioral and neurobiological consequences of repeated exposure to cocaine and cessation of cocaine treatment after chronic exposure. Studies are designed to provide information on tolerance, cross tolerance relationships, sensitization and withdrawal, and possible approaches for modulating these effects, both amplification and dampening.

To further characterize the supersensitivity that develops to opiate antagonists with respect to pharmacological specificity, the time course of development and recovery, and neurological mechanisms of action.

To characterize receptor specificity of anxiogenic drugs and benzodiazepine antagonists using schedule-controlled behavior and to delineate mechanisms of anxiogenic action when these drugs function as punishing stimuli.

To determine mechanisms of overlapping behavioral effects of nicotine and its metabolites and analogs, and to evaluate means of pharmacologically altering the reinforcing effects, discriminative stimulus effects and psychomotor stimulant or depressant effects of nicotine.

#### **Summary of Ongoing Research**

##### **A. Maintenance of Behavior by Drug Injections: Goldberg, S.R., Katz, J.L., Schindler, C.W. and Prada, J.A.**

Drugs of abuse can control large amounts of behavior by acting as either reinforcing stimuli to maintain behavior that leads to their administration, or by functioning as discriminative stimuli that are associated with conditions under which behavior is consistently reinforced by other relevant stimuli, such as presentation of food or avoidance of electric shock. In many situations, drugs of abuse probably function through multiple mechanisms to persistently sustain long sequences of drug-seeking behavior that may be very resistant to extinction. Schedule-controlled performances provide a meaningful way to analyze these long sequences of drug-seeking behavior in the same way as operant behavior maintained by other events such as food or electric shock.



In one series of experiments, groups of squirrel monkeys were trained to respond under a second-order schedule of either i.v. morphine injection (1.0 mg/kg/day), or food presentation. On this schedule, every 30th response (fixed-ratio 30) was followed by the presentation of a brief (2 sec.) stimulus light, and the first fixed ratio completed after the lapse of 60 min. was followed by a series of brief stimuli, each paired with a morphine injection or food presentation. Initially, neither substituting saline for morphine nor suspending food delivery (extinction) produced large decrements in rates of responding. However, when the brief stimuli were also removed during extinction, responding markedly decreased. After responding was reestablished with morphine or food and brief stimulus presentations, subsequent exposure to extinction conditions resulted in significantly reduced rates of responding, even with the brief stimuli present. Removing the brief stimuli also led to decrements in responding during continued morphine or food reinforcement. The degree of reduction was dependent on the dose of morphine, with larger reductions typically occurring at lower doses. The results point to the importance of the history of exposure to environmental stimuli paired with reinforcement as a determinant of the perseverance of drug-seeking behavior.

In cardiovascular studies, it was found that treatment with calcium channel blockers, such as nimodipine or verapamil, would reverse or prevent the changes in heart rate and blood pressure produced by cocaine. In order to assess the effects of these compounds on the behavioral effects of cocaine, studies are being conducted in squirrel monkeys trained to respond under fixed-ratio schedules of food presentation or i.v. cocaine injection. As the structure-activity studies of cocaine and its analogs have been completed in squirrel monkeys, additional investigations have been conducted to assess the effect of pre-session treatment with calcium channel blockers on cocaine-maintained behavior, or on food-maintained behavior that is suppressed by cocaine administration. In pilot experiments, pre-session treatments with 5-min. i.v. infusions of nimodipine that were sufficient to reverse cardiovascular effects of cocaine were found to be without effect on these other measures. In subsequent studies, an effort will be made to examine the effects of oral doses of these compounds; the oral route might be expected to provide longer-lasting activity which may be critical in behavioral experiments involving measurements over time spans of approximately 60 minutes.

**B. Suppression of Behavior by Drug Injections: Katz, J.L., Goldberg, S.R. and Prada, J.A.**

Many psychoactive drugs, including cocaine, nicotine and nalorphine, show an important duality shared with certain other types of stimuli: they can function effectively as positive



reinforcers or as punishers within the same dose range, depending on the context of environmental conditions. Systematic evaluation of the environmental conditions which determine the type and direction of behavioral effects with a variety of drugs may have practical implications for the control of licit or illicit drug use by humans. Initial studies demonstrated that nicotine can function either as a reinforcer to maintain behavior, or as a punisher (aversive or noxious stimulus) to suppress behavior, depending on the context in which it is administered. It was the object of this project to extend these studies to additional drugs under a variety of conditions.

Also, the initial studies replicated previous findings with histamine and nicotine using procedures which were modifications of the ones used previously. In subsequent studies, a variety of drugs was examined. Punishing effects were found for ethyl-B-carboline-3-carboxylate (B-ECC), buspirone, gepirone, yohimbine, and quipazine. Drugs that appear to lack specific punishing effects under this procedure are cocaine and midazolam.

Subsequent studies have been examining the punishing effects of B-OCE in more detail. These studies have shown that flumazenil antagonizes the punishing effects of B-OCE, and that this antagonism is dose-related. The functions that have been collected at this point will permit an analysis of the apparent  $pA_2$  for the effect. This will provide information that will be of use in determining the receptor mechanism by which these drugs are exerting their behavioral effects.

Studies have also concentrated on the punishing effects of quipazine. While the punishing effects of B-OCE have been antagonized by the benzodiazepine receptor antagonist, flumazenil, this compound was not found to antagonize the punishing effects of quipazine. Current studies are concentrating on the antagonism of the punishing effects of quipazine by the 5-HT<sub>2</sub> antagonist, ketanserin.

**C. Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals: Goldberg, S.R., Katz, J.L., Prada, J.A., Swedberg, M. and Schindler, C.W.**

General information on the behavioral pharmacology of a drug in a pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher as well as to establish a profile of behavioral effects produced by a given compound. Multiple schedules of food presentation with both fixed-interval and fixed-ratio components have been used most frequently in this type of study, since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. Second-order schedules

of food presentation are useful for comparative studies of behavior maintained by food presentation or i.v. drug injection, and may provide a particularly sensitive baseline for analyzing the rate-increasing effects of psychomotor stimulants such as cocaine.

The present project involves the assessment of both the acute and chronic effects of a variety of drugs under multiple or second-order schedules of food presentation in squirrel monkeys and rats. The drugs studied include psychomotor stimulants, such as cocaine, various cocaine analogs, nicotine, various nicotine metabolites and analogs, and caffeine. Since the behavioral effects of certain drugs depend on the type of event that maintains behavior, the effects of drugs are also studied on comparable performances maintained under fixed-interval schedules by either delivery of electric shock or by termination of a stimulus associated with electric shock. Finally, the discriminative stimulus effects of selected drugs, such as nicotine and cocaine, are explored with a focus on the actions of their metabolites and analogs.

These procedures provide stable, long-term sensitive baselines for quantitative assessment of both stimulant and depressant drug effects. The long-term nature of these baselines also makes them ideal for studying tolerance and cross-tolerance development to chronic treatment with various drugs, including cocaine, caffeine, adenosine analogs, and benzodiazepines, for studying the mechanisms of action by analyzing the outcome of pharmacological interaction studies using specific agonists and antagonists, and for studying the effects on behavior of various combinations of psychoactive drugs.

One set of experiments has been initiated to determine whether chronic use of cocaine will result in tolerance, and whether discontinuing that use will result in an observable withdrawal syndrome. Pilot data indicated that tolerance would develop to the effects of cocaine on second-order responding for food in squirrel monkeys and that an observable withdrawal syndrome may occur with discontinued use. Squirrel monkeys have been trained to respond on a fixed-interval (FI) 5 min. (FR 30:S), second-order schedule for food. Each session contains 8 FI segments, and there is no limited hold on either the FI or total session length. As such, when animals are given cocaine, even if a dose dramatically depresses responding, sessions continue until the animal receives all eight reinforcers. The results of pilot data indicated that this may be a crucial variable in the development of tolerance.

So far, data have been collected on the acute dose-effect curves for doses of cocaine ranging from 0.03 to 3.0 mg/kg. Cocaine at lower doses tends to increase response rates in this schedule, while higher doses depress responding during the initial FIs. Lower doses, which increase responding, have been tested chronically to determine



whether tolerance would develop to the rate-increasing effects of cocaine. However, the data from this experiment have been equivocal. One animal showed clear evidence of tolerance in that the rate-increasing effect of cocaine was diminished; however, there was no change in the dose which produced rate-decreasing effects. The other two subjects did not demonstrate clear changes in the rate-increasing effects of cocaine, nor did their dose-effects curves shift to a statistically significant degree during chronic treatment. Higher doses of cocaine are now being tested in a chronic regimen.

A second set of experiments was designed to evaluate the stimulation of operant behavior produced by cocaine and several of its analogs. The analogs were studied previously in the collaboration with the Neurosciences Branch to determine their relative activities as reinforcers of i.v. drug self-administration behavior as well as to quantitate their relative activities as uptake inhibitors in several transmitter systems. The results of this collaborative study indicated that inhibition of dopamine uptake was related to the potency of the drugs as reinforcers under fixed-ratio schedules of i.v. drug injection. Studies were then conducted to ascertain if the same relations would be obtained in assessing the psychomotor stimulant effects. Food-deprived, adult male squirrel monkeys and pigeons were used as subjects. Subjects were trained to respond under a multiple fixed-interval, fixed-ratio schedule of food presentation during daily experimental sessions. Doses of each drug were injected i.m. 5 min. before experimental sessions no more frequently than twice per week. Results to date are very preliminary; however, they suggest that several of the analogs have little efficacy as psychomotor stimulants. Since all of the drugs bind to the cocaine transporter, those drugs lacking efficacy will be tested further as antagonists of cocaine. For comparative purposes, the disruptive effects of these analogs is being examined on similar responding maintained under a simple fixed-ratio 30-response schedule of food pellet presentation. Under this schedule, several compounds have been tested and the following order of potency has been observed: cocaine > norcocaine > d-pseudococaine = l-pseudococaine > d-cocaine.

In a third series of experiments conducted in collaboration with Dr. Ian Stolerman of the Institute of Psychiatry, London, behavioral effects of d- and l-nicotine, d- and l-nornicotine, and l-cotinine were studied in two paradigms. In Experiment 1, rats responded under a multiple FI 5 min., fixed-ratio (FR) 20 schedule of food presentation. Aside from differences in potency and time course, the stereoisomers of nicotine and nornicotine produced qualitatively similar effects on rates of responding. With increasing doses of drugs, FI response rates first increased and then decreased, while FR response rates only decreased. In contrast, cotinine (up to 100 mg/kg) produced only dose-dependent increases in

FI response rates and had no effect on FR response rates. Rate-increasing effects of cotinine were not blocked by mecamylamine.

In Experiment 2, rats were trained to discriminate between l-nicotine (0.1 mg/kg s.c.) and saline (0.1 ml/kg s.c.) in a two-bar, operant conditioning procedure under a tandem variable-interval (VI) 1 min., FR 10 schedule of food presentation. Full generalization was obtained to d-nicotine and to l- and d-nornicotine. Generalization to cotinine occurred only with large doses that contained significant amounts of nicotine present as an impurity. There was no generalization to non-nicotinic drugs (i.e., morphine and clenbuterol), even at doses that reduced response rates. The rank order of potency for nicotine and its analogues was similar in experiments 1 and 2: l-nicotine was 10-20 times more potent than d-nicotine as well as the stereoisomers of nornicotine (which do not demonstrate stereoselectivity in the rat). Cotinine was at least several hundred times less potent than nicotine. Behavioral potencies correlated with previously reported concentrations of the analogs needed to reduce binding of tritiated nicotine to rat brain membranes.

**D. Comparative Studies of Drug Self-Administration in Squirrel Monkeys and Humans: Goldberg, S.R., Henningfield, J.E., Katz, J.L., Schindler, C.W., Lamb, R.J. and Heishman, S.**

Self-administration studies permit an assessment of the relative contribution of environmental and pharmacologic factors to the self-administration of drugs, as well as to changes in response to drug due to tolerance and sensitization. Parallel comparative studies in squirrel monkeys and humans, in which subjects are given the opportunity to self-administer comparable doses of cocaine, morphine and nicotine under similar behavioral schedules and experimental conditions, provide a means by which to assess the generality of biological variables influencing drug self-administration. These studies provide an opportunity to evaluate the role of environmental variables and the role of conditioning in human drug-taking behavior. In addition, these studies make it possible to investigate whether these roles differ from the roles of these variables in animal models of drug taking.

The studies conducted so far have shown that responding is maintained in human subjects in the same manner in which it is maintained in non-human experimental subjects. Additionally, behavior in humans and squirrel monkeys appears to be a function of similar variables. The stimuli that are associated with injections of cocaine develop conditioned reinforcing effects in humans in a manner similar to that in which these effects develop in squirrel monkeys. In humans, reinforcing effects of cocaine, morphine and nicotine can be detected at doses that do not occasion subjective reports of drug effects or drug-liking. These results indicate that reinforcing



effects of drugs can occur without traditional indications of abuse liability.

**E. Drug Effects on Classical Conditioning in Rabbits: Goldberg, S.R. and Schindler, C.W.**

In collaboration with Dr. John Harvey at the University of Iowa, the effects of opioids on classical conditioning have been studied in rabbits. This work has included the study of opioid peptides on classical conditioning using intraventricular injections of d-alaleu-enkephalinamide and also an analysis of 2-deoxy-glucose utilization during acquisition of conditioned responses in rabbits. In addition, a procedure has been employed to study locomotor activity in rabbits that provides a point of comparison to other more established procedures, particularly when reference is made to analyzing the effects of opioids on classical conditioning across different species. To date, the studies conducted indicate that the effects of opioids on locomotor activity in rabbits are more comparable to those seen in other species than the effects of opiates on classical conditioning. This suggests that fundamentally different opioid processes are involved in the classical conditioning paradigm in the rabbit.

In collaboration with Dr. Stanley J. Weiss of American University, studies have been conducted to investigate the effects of chlordiazepoxide (CDZ) on operant-conditioned inhibition in the rat. It has been suggested that one of the effects of CDZ may be the disinhibition of behavior. If this is the case, then one might predict that CDZ should have a much larger effect on responding during conditioned inhibition than responding in extinction which does not involve inhibitory processes. This possibility has been tested in rats responding on a schedule which includes both inhibition and extinction components, and it has been found that CDZ produces comparable effects on both extinction and inhibition responding, indicating that CDZ does not produce a selective effect on behavior inhibition.

**F. Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonist and Other...: Schindler, C.W., Goldberg, S.R. and Katz, J.L.**

While it has been known for some time that chronic opioid antagonist treatment will produce behavioral supersensitivity in squirrel monkeys, the effect of opioid antagonist treatment in rats has been less clear. Thus, this project investigated this phenomenon in rats using a cumulative dosing procedure in which a single dose-effect function (1 - 100 mg/kg) can be determined in a single session. Initially, only a dose of 100 mg/kg naltrexone was found to affect fixed-ratio responding for food. However, even with naltrexone administered only once per week during the determination of the dose-

effect function over a period of 8 weeks, it was found that a dose as low as 10 mg/kg produced a complete cessation in responding. This effect was found to be long-lasting, persisting over a period of 10 weeks after the cessation of naltrexone administration.

Further, this effect does not appear to be related to a learning phenomenon since a dose of 10 mg/kg, administered after saline injections only, was found to produce an effect similar to that which occurred following cumulative doses of 1 and 3 mg/kg of naltrexone. In addition, it has been reported previously that chlordiazepoxide will partially antagonize the supersensitivity seen in squirrel monkeys; however, this does not appear to be the case in rats. In contrast, morphine pretreatment was found to produce some antagonism of the sensitivity. In view of this, collaborative studies are underway with Dr. T.-P. Su (Neuroscience Branch) in an effort to determine whether the supersensitivity observed on behavior is correlated with changes in opioid receptors in the brain. Finally, studies are underway to test the effects of pre-session injections of the opioid antagonist naltrexone on morphine-maintained behavior using long, second-order schedules in which responding during experimental sessions is maintained by brief stimuli that are associated with morphine injection only at the end of daily sessions. Since all the morphine is given at the end of the session, it is assumed that any effect of naltrexone may be attributed to an effect on morphine-maintained responding, rather than a more direct effect of morphine itself.

**G. Abuse Liability and Behavioral Effects of Benzodiazepines: Katz, J.L., Witkin, J.M., Griffiths, J.W., Spear, D. and Prada, J.A.**

Benzodiazepines are among the most widely prescribed classes of drugs. The widespread use of these compounds leads to concerns regarding their possible abuse. The present studies are designed to provide a characterization of the conditions that may promote benzodiazepine abuse as well as information relevant to the mechanisms of benzodiazepine action and dependence. Specific areas addressed in these studies are: (a) receptor specificity of various actions of benzodiazepines, including ataxic, anxiolytic, anticonvulsant and dependence-producing effects; (b) anxiogenic actions of benzodiazepine-receptor inverse agonists; and, (c) dependence on benzodiazepines and possible pharmacological management of the withdrawal reaction.

With respect to studies concerned with the receptor specificity of the actions of benzodiazepines, a series of studies will be initiated to characterize benzodiazepine (Bz) receptor subtype-specific effects of Bz agonists. The antianxiety, anticonvulsant, and ataxic behavioral actions of Bz agonists will be antagonized by the relatively pure Bz antagonist, flumazenil. Effects of diazepam, chlordiazepoxide, zolpidem, CGS 9896, halazepam,



quazepam, lorazepam, and triazolam will each be studied in combination with several doses of flumazenil. In addition, in some studies, several antagonists will be studied including B-CCE, flumazenil, CGS 9B95, B-OCT, and 3-methoxy-B-carboline. These antagonists are chosen because they have been reported to have specific actions that may be related to selective antagonism at subtypes of benzodiazepine receptors. For each of the effects described below, a  $pA_{50}$  analysis of the effects of flumazenil will be conducted in order to determine if the effects of the various agonists are mediated by different receptor mechanisms.

**Concerning the antianxiety effects,** subjects are trained to press a response key for food reinforcement in a two component schedule. In one component, a red light is presented, and each thirtieth response produces a food pellet. In the second component, the light is absent and each thirtieth response produces a food pellet and, in addition, the first of the thirty responses produces an electric shock. Five components of each type comprise an experimental session. The number of shock presentations delivered to the subject depends upon his behavior; the more frequently the subject responds, the more frequent the shocks. Subjects are trained until performances are stable, after which the effects of the various drugs are assessed by injecting before sessions.

**Concerning the ataxic effects,** the apparatus used for the inverted screen test to evaluate motor ataxia consists of four 15 x 15 cm. pieces of wire mesh mounted 15 cm. apart on a rod, 35 cm. above the table top. For each trial, one mouse is placed on each screen and the rod is rotated 180 degrees over 10 sec. Mice which fail to climb to the top of the screen within 60 sec. are scored as ataxic. Each mouse is injected with a drug and twenty minutes later given a test trial. The mice are then injected with antagonists and retested 10 min. later.

**Concerning evaluation of the anticonvulsant effects,** each mouse is injected with a dose of an agonist followed 20 min. later by a dose of antagonist or vehicle. After an additional 10 min., the mice are injected with 80 mg/kg of pentylenetetrazole. Mice which do not develop clonic convulsions within 5 min. of receiving pentylenetetrazole are scored as being protected by the agonist.

**Concerning evaluations of dependence to benzodiazepines,** in these studies, subjects (mice or rats) will be given agonists orally until tolerance develops, followed by precipitation of withdrawal by administration of the various "selective" antagonists. Withdrawal is assessed in accordance with published procedures, as well as using disruptions in ongoing operant behavior as criteria.

Studies of the effects of a series of benzodiazepine antagonists were conducted in nontolerant and chlor-diazepoxide-tolerant rats. These studies showed that supersensitivity developed to the effects of the antagonists, flumazenil, CGS 9895, and B-OCT, but not B-OCE. Additionally, obvious signs of precipitated withdrawal were observed only after administration of flumazenil. These results suggest that there may be a heterogeneity in the effects of benzodiazepine antagonists. Further, these results imply that, in contrast to some currently accepted hypotheses, the inverse agonist may be acting at a site that is distinct from that at which the pure antagonists act, or that the inverse-agonist activity that is observed in nontolerant subjects is mediated through a nonbenzodiazepine receptor site.

Studies have also been initiated to investigate the discriminative effects of benzodiazepine receptor ligands. In these studies, rats or pigeons are trained to discriminate the effects of the inverse agonist, B-OCE, or the relatively pure antagonist, flumazenil. Notably, a study conducted using a standard procedure to develop drug discriminative control was not successful using B-OCE as the training drug. Thus, a study is planned which will employ a conditioned taste-aversion procedure to develop discriminative control with this compound. Once discriminative performance is established, a variety of drugs will be tested for discriminative effects similar to those of the training drug. Subsequently, subjects will be made tolerant to the effects of benzodiazepine agonists, and evaluated both for a possible shift in the B-OCE dose-effect curve and the effects of the drugs studied previously. It is hoped that these experiments will shed light on the set-point hypothesis about benzodiazepine receptor function in tolerance and dependence.

Discriminative control has been developed with flumazenil. However, the preliminary results of these studies available indicate that benzodiazepine agonists do not share discriminative effects with flumazenil, confirming the purity of the antagonist actions of this compound and suggesting the pharmacological specificity of the discriminative effect that was established.

With respect to studies of the pharmacological management of the withdrawal reaction, these will examine possible treatment approaches for benzodiazepine withdrawal. In this regard, several studies have suggested that the degree of dependence/tolerance on benzodiazepines is decreased immediately following recovery from withdrawal precipitated by the benzodiazepine antagonist, flumazenil. Thus, initially an attempt will be made to replicate



these findings. Subsequently, an attempt will be made to hasten the course, or dampen the degree of withdrawal following cessation of benzodiazepine administration through the use of various pharmacological treatments.

#### H. Behavioral Pharmacology of Non-Opioid Analgesics: Goldberg, S.R. and Swedberg, M.

The pharmacological mechanisms of action of potential non-narcotic analgesic compounds have been studied using a drug discrimination paradigm, a behavioral procedure which has evolved to become a major in vivo behavioral assay in pharmacology, due to its demonstrated sensitivity in differentiating among drugs from different pharmacological classes. Operant rat chambers, enclosed in light- and sound-attenuating, fan-ventilated enclosures, are used. The chambers are equipped with two response levers, a white house light and a dim red light. Scrambled electric shocks can be delivered to the grid floor of the chamber by a constant current shock generator. Rats are trained under a fixed-ratio 5 (FR 5) schedule of stimulus shock termination to respond on one lever after an i.p. injection of promising non-narcotic analgesic compounds and on the other lever after an i.p. injection of vehicle.

In a series of discrimination studies completed this year, rats were trained to discriminate intraperitoneal injections of either flupirtine (10.0 mg/kg) or D-16949 (2.0 mg/kg), non-opioid analgesics in clinical use or development in Europe, from the vehicle no-drug condition in a two-choice, shock avoidance procedure. Putative agonists were substituted for the training drug, and putative antagonists were administered in combination with the training drug, respectively. Results indicate alpha-2 adrenergic mechanisms to be of primary importance in mediating the discriminative effects of flupirtine. Opiate mechanisms have been eliminated on the basis of the non-substitutability of opioid analgesics and lack of effect of the opiate antagonist, naltrexone. With D-16949, tests with opioid analgesics, phencyclidine, d-amphetamine and lysergic acid diethylamide (LSD) indicate that there is a lack of any measurable similarities in terms of discriminative effects. Of note, tests with serotonergic agonists and antagonists suggest that 5-HT-1B mechanisms may be of primary importance for mediating the discriminative effects of D-16949.

#### I. Cardiovascular Changes Induced by Cocaine in Squirrel Monkeys: Goldberg, S.R., Schindler, C.W. and Rao, S.T.

Over the past few years, there has been an increase in the number of deaths due to cocaine abuse. Many of these deaths have been related to the effects of cocaine on cardiovascular function. Thus, the effects of cocaine on cardiovascular function are being investigated in squirrel monkeys with chronic indwelling catheters in the iliac

artery and vein. Heart rate and blood pressure can be measured from the arterial catheter, and cocaine or other drugs can be delivered through the venous catheter. In addition, electrocardiograms (EKGs) may be obtained simultaneously with these other measures.

The results indicate that cocaine produces an immediate increase in mean blood pressure of approximately 10-20 mm at higher doses (1.0-3.0 mg/kg). This increase in pressure is accompanied by a decrease in heart rate of 10-30 beats/min. at these higher doses. The increase in blood pressure remains above baseline levels for at least 30 min. following the cocaine injections, while the heart rate returns towards normal within about 15 min. There is a tendency for the heart rate to increase 15-30 min. following the cocaine injections, particularly at lower doses (0.3-1.0 mg/kg). In this regard, it was found that haloperidol (0.01-0.03 mg/kg) will partially antagonize the effects of cocaine on blood pressure and heart rate, although this effect is not as dramatic as that seen with the calcium channel antagonists, nimodopine or verapamil.

Finally, a tendency of cocaine to induce arrhythmias has been observed in some squirrel monkeys at the higher doses of cocaine. These results corroborate that cocaine has clear and dramatic effects on cardiovascular function in squirrel monkeys at doses comparable to those which maintain self-administration behavior. As such, this appears to be a reasonable model for studying the effects of cocaine on cardiovascular function. In the next few months, an effort will be made to investigate more fully the pharmacological mechanisms of cocaine's effects and to test a number of different drugs for their antagonist properties.

**J. Behavioral Pharmacology and Toxicology of Psychomotor Stimulants:  
Witkin, J.M., Goldberg, S.R., Katz, J.L. and Schindler**

This project involves evaluating the behavioral effects of psychomotor stimulants in order to characterize the complex and diverse pharmacology of these compounds as well as to document the range of behavioral and toxic actions which accompany acute and prolonged administration of these compounds. Different routes of administration are employed in rodent and primate species, recognizing the marked differences in the spectrum of effects observed across different routes and species. Compounds currently under investigation include cocaine and cocaine analogs, methamphetamine, d-amphetamine, and N,N-dimethylamphetamine. Experiments with these drugs are integrated with other ongoing work in the Branch involved with examining the patterns of self-administration, the physiological actions, and the genetic factors which may be associated with these compounds as well as those of methoxylated amphetamine derivatives.



Evaluation of pharmacological means of altering behavioral and toxic effects of cocaine and related compounds is a key research problem in this area. Focus is currently on dopaminergic drugs, muscarinic agents, and calcium channel antagonists. In this regard, unique contributions seem likely to come from the planned detailed analysis of dopamine and muscarinic receptor subtype pharmacology. The recent and ongoing development of highly selective ligands has made possible, for the first time, refined analysis of the role of these receptors in behavioral function, as well as in the diverse and enigmatic effects of cocaine and related compounds. For example, rats and squirrel monkeys are being studied under multiple schedules of food presentation in which increases and decreases in responding by cocaine can be studied.

To further delineate the role of receptors which may mediate the effects of cocaine and related compounds, drug-interaction studies will be used to help determine the involvement of dopamine receptor subtypes in both the behavioral stimulation and depression produced by cocaine. Thus, not only will an effort be made to establish a dopaminergic role for specific behavioral effects of cocaine, but also an effort will be made to produce pharmacological separation of the rate-increasing and the rate-decreasing effects of this compound. Preliminary results with squirrel monkeys suggest that the behavioral depressant effects of cocaine may be unresponsive to the classic dopamine (D2) antagonist, haloperidol, and to the D1 receptor antagonist, SCH 23390. In contrast, however, the cardiovascular effects of cocaine appear to be at least to some extent antagonized by haloperidol. In this regard, it is hoped that the data from these studies will be important in defining the range of behavioral effects of cocaine that are altered by dopaminergic compounds; haloperidol, for example, appears to block the discriminative stimulus effects of cocaine but may have little activity against the depressant effects.

Another series of studies is being conducted to define the involvement of muscarinic receptors in the rate-enhancing effects of cocaine in rats and squirrel monkeys. It is hoped that these studies will also help to differentiate behavioral enhancing from behavioral depressant actions of cocaine and that the data generated will interface with the Branch's ongoing efforts investigating the interrelationships between the behavioral and cardiovascular effects of cocaine. In this project, responding of both species is maintained under multiple schedules of food presentation in which it has been possible previously to observe both response rate increases and response rate decreases across a range of cocaine doses. Preliminary evidence suggests that pharmacologically specific modulation of cocaine's behavioral effects is possible. The benzilate antimuscarinic, benactyzine, appears to potentiate the rate increases produced by cocaine and may also be effective in

reversing the rate-decreases induced by cocaine. Thus, studies with squirrel monkeys are underway.

The behavioral and neurobiological consequences of chronic drug administration also comprise a large part of the Branch's ongoing research efforts. Focus in this area is on the determinants of behavioral and neuropharmacological actions associated with repeated drug exposures and the cessation of chronic drug administration. It is anticipated that critical information on tolerance and cross-tolerance relationships, as well as about sensitization and withdrawal will be forthcoming from this area of inquiry. Modulation of these effects, both amplification and dampening, will be examined. One study was recently undertaken to assess the mechanism by which cocaine exerts its behavioral effects through studies of tolerance and cross-tolerance. The behavioral effects of cocaine are being determined in drug-naive subjects, as are the effects of specific D1- and D2-receptor agonists. Once the acute effects of these drugs are documented, subjects will be rendered tolerant to the behavioral effects of cocaine and the effects of the various drugs redetermined. If the effects of cocaine are found to be mediated by specific dopaminergic receptors, it might be expected that cross tolerance will be exhibited only by those agonists demonstrating a similar profile of activity.

Food-deprived, experimentally-naive rats are trained to press a response key with food reinforcement under a fixed-ratio schedule of food presentation. During sessions, the effects of the various compounds investigated will be assessed in terms of cumulative dose rather than acute doses administered. For comparisons of dose-effect curves, analysis of variance and linear regression techniques will be used to determine the  $ED_{50}$  value for each compound (i.e., the dose causing a decrease in response rates to 50 per cent of the control rate) and 95% confidence limits. Body weights will also be determined daily, and followed for some time after termination of cocaine treatment in an attempt to document any withdrawal effects. In addition, behavior will be monitored for any withdrawal effects. Moreover, additional plans are being made to evaluate the neuropharmacological consequences of chronic cocaine at the molecular level. Combined with cross-tolerance data, this overall approach could permit an integrated analysis of the myriad of effects induced by daily administration of cocaine.

Dose-effect functions for various psychomotor stimulants, selective dopaminergic agonists, and other drugs of abuse have been determined. However, attempts to document the development of tolerance to the behavioral effects of cocaine have so far been unsuccessful. Thus, various treatment regimens will be systematically evaluated in an effort to develop tolerance to cocaine and to more precisely define the conditions under which this tolerance develops.



Another focus of this line of experimental inquiry involves the toxicity of psychomotor stimulants. Convulsions and death are important features of the effects of these drugs. In addition, for some of these compounds, it is now well documented that neurotoxicity, in the form of long-term neurotransmitter depletion and neuronal degeneration, is produced by even short-term exposure. Thus, experiments will be designed in an attempt to evaluate these toxic actions, to delineate the mechanisms responsible for these effects, and to establish methods for preventing or reversing psychomotor stimulant-induced toxicity.

Along these lines, a study has already been designed in an effort to assess the relative contribution of different receptor systems to the lethal effects of cocaine. Thus,  $LD_{50}$  values will be determined for cocaine alone and in combination with various agents. In particular, dopaminergic receptor subtype-specific antagonists will be studied, since several actions of cocaine have been shown to be modified by classical dopaminergic antagonists. In this regard, the availability of relatively selective receptor subtype ligands makes further clarification of the involvement of dopamine neurotransmission in cocaine toxicity possible. By examining changes in cocaine dose-effect curves, the contribution of various systems to the lethal effects of cocaine may be assessed. Moreover, in order to verify the selectivity of the antagonists, in some cases an effort will be made to document their interaction with subtype-selective agonists. The drugs to be studied include: haloperidol, SCH 23390, SKF 38393, (-)-NPA, YM 09151-2, fenoldopam, atropine, pergolide, and spiperone.

Preliminary results are available which indicate that the lethality function is steep, but that it exhibits a plateau such that some animals survive even very high doses. In this regard, an initial experiment conducted was quite intriguing, pointing to stimulation of D<sub>1</sub>, but not D<sub>2</sub>, dopamine receptors as targets of cocaine-induced lethality. In contrast, the D<sub>2</sub> receptor antagonist, haloperidol, blocked the lethality of N,N-dimethylamphetamine, but not that of cocaine.

Experiments are now underway to help define the potential neurotoxicity of sublethal doses of psychomotor stimulants. A series of rats have been treated with either cocaine (10 or 20 mg/kg, intraperitoneally, twice a day for 7 days), or N,N-dimethylamphetamine (25 or 50 mg/kg, subcutaneously, twice/day for 4 days). Two weeks after the final treatment, brains were rapidly removed and dissected on ice for subsequent determination of neuronal and neurotransmitter degeneration. Further studies are planned with other psychomotor stimulants and potentially protective agents.

In concert with ongoing studies on psychomotor stimulants, experiments which evaluate the discriminative stimulus effects of these drugs are also planned or underway. Rats are trained to discriminate intraperitoneal (i.p.) injection of cocaine (10 mg/kg) from saline, and the ability of other compounds to produce similar discriminative effects, or to prevent the discriminative stimulus effects of cocaine will then be ascertained. Selection of compounds for these purposes will be guided by results from other ongoing studies. Four squirrel monkeys are also being trained to discriminate intravenous cocaine from saline. Since the route of administration can be an important determinant of the subjective effects of these drugs, it will be of interest to explore various routes, such as inhalation.

**K. Behavioral and Neurotoxic Effects of Substituted Amphetamines:**  
Katz, J.L., Witkin, J.M. and Shores, E.

The present studies are designed to examine the behavioral effects of substituted amphetamines that may contribute to drug abuse and how those effects may relate to neurotoxic actions of the drugs. The specific objectives of this project are:

(a) To study the reinforcing effects of i.v. drug injections scheduled as consequences of behavior. Various substituted amphetamines, as well as other reference drugs of abuse, will be examined using fixed-ratio schedules of drug injection.

(b) To evaluate the effects of these compounds on operant behavior in standard procedures in which subjects are trained to respond under schedules of reinforcement during daily experimental sessions. Once performances are stable, the effects of the drugs will be assessed using routine pre-session injections.

(c) To assess the neurotoxic effects of these compounds using standard techniques.

The long-term objectives of this research include evaluation of the abuse liability of various substituted amphetamines, to better define the duration of the neurotoxic effects of (+)3,4-methylenedioxymethamphetamine (MDMA) in the primate, and to develop functional correlates of neurotoxicity by assessing the effects of drugs active on serotonergic systems before and after a regime of MDMA.

With respect to the evaluation of the reinforcing effects of these compounds, subjects are surgically prepared with chronic venous catheters and trained to self-administer cocaine under a fixed-ratio 30-response schedule of reinforcement. After subjects respond reliably, cocaine and saline injections are alternated across

sessions until the subjects consistently respond at high rates when cocaine is administered, and at low rates when saline is administered. Once performances are stable, the cocaine solution is replaced with a test solution during selected experimental sessions to determine the extent to which any given test-drug maintains drug-taking behavior.

Preliminary results are as follows. Responding was well maintained by the (+)-isomer of MDMA, with maximal rates of responding at a dose of 0.3 ug/kg/injection. In contrast, responding was not well maintained by racemic MDMA, however, based on the results with the (+)-isomer, it would be worthwhile to study the higher doses further. The (-)-isomer has not yet been studied. Preliminary results in a few subjects suggest that the (+)-isomer of MDA also was without significant effects in maintaining behavior. Finally, preliminary results have also been obtained with (+)-N,N-dimethylamphetamine, a designer drug for which there have been recent incidents of abuse. This drug maintains maximal rates of behavior at a dose of 3.0 ug/kg/injection. Subsequent studies will assess its relative potency compared to its close analog, methamphetamine.

With respect to evaluation of the effects of these compounds on operant behavior, food-deprived subjects (squirrel monkeys, rats or pigeons) are trained under fixed-ratio schedules of reinforcement. Once performances are stable, the effects of various drugs are assessed by administering injections in cumulative doses during experimental sessions.

Ongoing studies are comparing the effects of methamphetamine and (+)-N,N-dimethylamphetamine. While methamphetamine was found to decrease rates of responding at doses as low as 1.0 mg/kg, doses of N,N-dimethylamphetamine as high as 30.0 mg/kg were found to be without significant effects. This indication of relative potency is surprising, since the two drugs were approximately equipotent in producing lethality.

Effects of several drugs will be assessed in squirrel monkeys, before and during recovery from treatment with MDMA, which at relatively high doses has toxic effects on serotonergic neurons. A dose of 5.0 mg/kg (s.c.) of (+)-MDMA will be administered twice daily to monkeys for 4 consecutive days. Subjects will then be allowed various post-drug survival times, during which the effects of drugs active on serotonergic systems will be assessed. In addition to assessing drug effects, cerebrospinal fluid (CSF) will be collected by means of cervical puncture. Subsequent neurochemical studies will be conducted to measure the concentrations of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) in brain tissue samples. Anatomical studies to be pursued include quantitation of cell counts in the raphe nuclei of the brainstem, as well as immunocytochemical studies of serotonergic nerve fibers in the forebrain. It is hoped



that these studies will identify a functional indicator of the postulated serotonergic deficit that may be applicable to the evaluation of such a deficit in human MDMA abusers.

## 2. Section on Behavioral and Biochemical Genetics

### Overview

This Section conducts behavioral, biochemical and pharmacogenetic studies using primarily animals models to investigate the contribution of genetic factors to drug abuse, the central mechanisms of drugs of abuse, and the commonality between various drug-related behaviors. This Section also conducts rodent breeding programs to provide the Addiction Research Center (ARC) with genetically-specified animal populations for use in studies of drug abuse.

The overall present and future goals of this Section are: (1) to determine the extent to which genetic factors mediate substance abuse; (2) to identify specific gene loci related to substance abuse; and, (3) to provide the ARC with a program in genetics to support the Institute's objectives in this area.

The general aims of this Section over the next several years are to systematically extend the ongoing research and to develop new projects in an effort to establish a significant pharmacogenetic database in the area of both drug sensitivity and operant drug self-administration.

More specifically, the aims of this Section are:

To produce a comprehensive genetically- and operantly-defined database of drug self-administration parameters developed with two commonly utilized rodent species, mice and rats, which can be subsequently incorporated into studies examining the biochemical and environmental mediators of drug self-administration.

To produce a similarly defined database of acute drug effect parameters using the same genetically-defined strains of rats and mice, to facilitate making comparisons between the effects of drugs on operant responding and other phenotypes relevant to acute responses to drugs.

To determine, through the use of genetic correlations and other genetic methods such as Mendelian analysis, quantitative estimates of genetic contributions to drug effects as well as the relationship between drug self-administration and other drug-related variables, such as initial sensitivity, and to ascertain the degree of common genetic control among these factors.

To conduct, through studies within the Branch and through collaborative efforts with other ARC neurochemists, systematic studies concerning the biochemical and molecular substrates of drug effects, particularly drug-seeking behavior.



Where genetic differences in response to a drug have been shown to result from a small number of genes, to coordinate the elucidation of those gene loci and gene products through joint studies between Behavioral Genetics personnel and other ARC molecular biologists.

#### Summary of Ongoing Research

##### A. Genetic Factors in Acute Response to Drugs: George, F.R. and Goldberg, S.R.

Studies of strain analysis of the acute changes in locomotor activation produced by cocaine have been completed in five rat stocks and twelve mouse stocks. In addition to the expected differences in potency and efficacy, four other novel findings were generated from this project. First, a rat strain (NBR) has been identified which shows an extreme activation response to cocaine, with scores approaching one order of magnitude greater than any other rat strains tested. Second, a mouse line, the LS/Ibg, has been found which exhibits no cocaine-induced increases in activity across a wide range of doses. The identification of these outlying genotypes is important since it provides an effective tool for elucidating the biochemical substrates which may underlie cocaine's activating effects. Third, it has been found that mice, but not rats, exhibit a low dose decrease in locomotor response to cocaine which is genotype-dependent. Interestingly, the strain rank order (SRO) of this low dose decrease is such that it suggests the possibility that a single gene, or a very limited number of genes, may be involved in the mechanism subserving this effect. Fourth, a mouse strain, the C57BL/6J, has been identified which demonstrates a severe and unique seizure response to cocaine. Interestingly, a closely related strain, the C57BL/6ByJ, does not show this response. The strain rank order (SRO) data, as well as the initial data from F1 crosses, suggest that the unique responses observed in the LS/Ibg and C57BL/6ByJ mice are due to a very small number of genes.

In addition, a strain analysis has been completed of the acute changes in locomotor activation induced by amphetamine in four rat strains. These strains show large differences in potency and efficacy in response to acute injections of amphetamine. Importantly, the SRO of the response to amphetamine is different from the SRO of the response to cocaine, indicating that the mechanisms of behavioral activation of response to these two stimulants may be associated with different neuronal sites.

Moreover, the effects of morphine on locomotor activity have been studied in seven mouse genotypes, and large differences have been found in the behavioral activating and behavioral depressant effects of morphine. In addition, genotypes have been identified which exhibit no behavioral activating response to morphine; this may

provide a valuable tool for elucidating the mechanisms underlying this behavior.

Also, the effects of prenatal treatment with cocaine have been investigated with respect to fetal mortality, birth weight, and behavioral development. The results obtained to date indicate that prenatal treatment with cocaine (30 mg/kg twice daily) may produce dramatic deficits in fetal survival, as well as large decreases in body weight and litter size, and decreased developmental progress. Significant genetic differences were also found in the expression of these effects. That is, some strains were found to be severely affected, while others were only mildly affected, or not affected at all.

Cocaine administered intravenously (i.v.) or intraperitoneally (i.p.) produces dose-related changes in spontaneous locomotor behavior. However, the extent to which orally (p.o.) administered cocaine affects locomotor activity, and how the potency and efficacy of oral administration compared to effects seen using the intraperitoneal route were not known. Thus, an effort was made to determine the relative effects of cocaine on ambulatory behavior depending upon whether the intraperitoneal or oral routes were used. With the intraperitoneal route of administration, dose-related increases in locomotor activity were observed, with significant increases beginning at 10 mg/kg and activity peaking at 30 mg/kg. Some seizures were noted at 56 mg/kg. With oral administration, a significant decrease in activity was observed at 3 and 10 mg/kg, with modest increases in activity seen at 10 and 30 mg/kg, and a statistically significant increase at 75 mg/kg. There were no seizures observed in mice administered cocaine orally. While both routes of administration were associated with increases in activity, there was a significant shift to the right in the dose response curve for orally-administered cocaine as compared to intraperitoneally-administered cocaine.

Sensitization to the effects of cocaine on locomotor activity has been reported to occur with repeated dosing. Since self-administration studies involve repeated exposures to orally delivered cocaine, an effort was made to determine the effects of chronic oral administration of cocaine on locomotor activity. In addition, studies were conducted to determine if sensitization occurred with repeated, orally-administered cocaine, since it was not clear if repeated administration of low doses of cocaine would enhance, reverse or not affect the initial decreases in locomotor activity observed in the previously mentioned experiments. The results indicated that there were differences in both the initial response and the direction of the sensitizing effect as a function of the oral dose of cocaine. At the lowest dose, 3 mg/kg, a significant decrease in locomotor activity was observed on the first day of testing. However, across days no statistically significant changes



in activity were seen, suggesting that no sensitization had occurred. Six mg/kg of cocaine via the oral route was associated with an initial decrease in locomotor activity, and a statistically significant degree of sensitization to this effect was seen with chronic dosing. This sensitization effect declined over time. At 10 mg/kg the locomotor activity scores on Day 1 were not different from control; however, there was a statistically significant decrease in activity observed across days, suggesting that a sensitizing effect had occurred. At 30 mg/kg an initial increase in activity was seen, and this effect was significantly enhanced across days.

**B. Genetic Factors in the Reinforcing Effects of Drugs: George, F.R. and Goldberg, S.R.**

An important component of the Behavioral and Biochemical Genetics Section relevant to the mission of the ARC is the study of genetic factors influencing animal models of drug-seeking behavior. Most self-administration studies with drugs other than alcohol have used the intravenous route for administration of the drug. However, because of the large number of animals required for genetic studies, it was important to develop other, less invasive and longer-lasting models of self-administration. Drawing upon experience with models of ethanol self-administration, procedures were developed for oral delivery of cocaine, etonitazine (ETZ), a potent, orally effective opiate agonist, and amphetamine.

These studies have generated the following findings:

(a) There are large genetic differences in the reinforcing efficacy of ETZ. In particular, LEWIS rats exhibit high levels of responding for ETZ under a variety of conditions, while F344 rats do not exhibit consistent patterns of responding for ETZ, regardless of the condition or training procedure used. This report may be the first to demonstrate in a systematic manner that reinforcement from drugs, other than alcohol, is influenced to a statistically significant extent by genetic factors.

(b) Cocaine can be established as a positive reinforcer using the oral route of administration. This project used previously-established ethanol-maintained behavior to implement a cocaine substitution procedure in C57BL/6J mice. Orally-delivered cocaine was found to maintain responding under intermittent schedules of reinforcement as well as responding associated with the vehicle. These results may provide one of the first reports of reinforcement associated with orally-delivered cocaine and may prove valuable in suggesting an alternative route of administration for cocaine, as well as a



novel species with which to investigate environmental and biological components of the behavior associated with self-administration of cocaine.

(c) The procedures developed for oral self-administration of cocaine are now being used to examine the relative efficacy of orally-delivered cocaine as a reinforcer in several strains of rats. Importantly, the same strains are being used that are examined in the locomotor activity studies in an effort to develop a comprehensive pharmacogenetic database of value for researchers interested in the studying the genetic substrates which may underlie certain facets of substance abuse. In addition, these same strains are also being used in a project examining the reinforcing properties of cocaine using the intravenous route. It is hoped that the results from this project will integrate well with existing data on intravenous cocaine self-administration, and make it possible to compare results obtained using the i.v. route with those generated using the oral route.

The results obtained to date from this study indicate that substantial genetic differences exist with regard to cocaine-reinforced behavior. Some strains will lever press to obtain significant amounts of cocaine at fixed ratios up to and including 64. In contrast, other strains extinguish responding for cocaine when the fixed ratio is increased above 2. The results also suggest that there are drug concentration effects which correlate well with the genetic differences in sensitivity to cocaine seen in the locomotor activity studies.

#### **C. Establishment of a Rodent Breeding Facility for Genetically-Defined Rats and Mice**

A third accomplishment of the Behavioral and Biochemical Genetics Section has been the establishment of a rodent breeding facility within the Institute which is providing ARC staff with several hundred genetically-defined rats and mice per month. The genotypes are chosen on the basis of their relevance to studies of substance abuse, that is, either they have been studied in other drug abuse-related research, or are genetically unique with regard to a trait of interest to researchers at the ARC. Moreover, genetic crosses of rodent strains known to differ in responses to cocaine are being conducted in an effort to determine the mode of transmission of the genes responsible for mediating sensitivity to, and reinforcement from, cocaine.

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## Publications (Cont'd)

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Weiss, S.J., Panlilio, L.V. and Schindler, C.W.: Selective attention and hedonics: The stimulus-reinforcer interaction re-evaluated. Psychonomic Soc. Bull., 1987.

## Abstracts (Cont'd)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00001-04 BPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Maintenance of Behavior by Drug Injection		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	S.R. Goldberg	Chief BPL, ARC, NIDA
Others:	J.L. Katz	Research Psychologist BPL, ARC, NIDA
	C.W. Schindler	Staff Fellow BPL, ARC, NIDA
	J.A. Prada	Research Psychologist BPL, ARC, NIDA
COOPERATING UNITS (if any) None		
LAB/BRANCH Preclinical Pharmacology Branch		
SECTION Behavioral Pharmacology Laboratory		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 1.30	PROFESSIONAL: 1.00	OTHER: 0.30
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Schedule-controlled performances provide a meaningful way to analyze drug-seeking behavior in the same way as operant behavior maintained by other events such as food or electric shock. In the present project with squirrel monkeys and rhesus monkeys, the rates and patterns of responding maintained by various drugs, including cocaine, nicotine, methohexital, MDMA and MDA, morphine, and chlordiazepoxide are being compared. Simple fixed-ratio and fixed-interval schedules and complex second-order schedules with brief stimulus presentation are used so that the role of brief stimuli in maintaining extended sequences can be assessed. The effects of pre-session treatments with a range of doses of pharmacologic agonists and antagonists, such as caffeine, specific D-1 and D-2 dopamine antagonists, serotonergic reuptake inhibitors, alpha-adrenergic antagonists, and calcium channel blockers, will be studied on responding maintained by intravenous psychomotor stimulant injection or food presentation under fixed-interval, fixed-ratio, and second-order schedules. The interactions of naloxone or naltrexone with behavior maintained under extended second-order schedules of morphine self-administration or food presentation will be explored.		

### Maintenance of Behavior by Drug Injection

These experiments with long second-order schedules in which drug is injected only at the end of the session will be extended to include studies of the reinforcing effects of other drugs including benzodiazepines and barbiturates. Studies of pharmacological and environmental means of weakening established behavior maintained by different drugs will be continued.

### Publications

Goldberg, S.R. and Henningfield, J.E.: Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of IV drug injection. Pharmacol. Biochem. Behav. 30(1): 227-234, 1988.

Goldberg, S.R., Schindler, C.W. and Lamb, R.J.: Second-order schedules and the analysis of human drug-seeking behavior. Drug Develop. Res., 1988, In press.

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Katz, J.L. and Goldberg, S.R.: Preclinical assessment of abuse liability of drugs. Agents Actions 23: 18-26, 1988.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA00002-04 BPL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Suppression of Behavior by Drug Injections

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J.L. Katz Research Psychologist BPL, ARC, NIDA

Others: S.R. Goldberg Chief BPL, ARC, NIDA

J.A. Prada Research Psychologist BPL, ARC, NIDA

## COOPERATING UNITS (if any)

None

## LAB/BRANCH

Preclinical Pharmacology Branch

## SECTION

Behavioral Pharmacology Laboratory

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.35

## PROFESSIONAL:

1.15

## OTHER:

0.20

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Many psychoactive drugs, including cocaine, nicotine and nalorphine, show an important duality shared with certain other types of stimuli: they can function effectively as positive reinforcers or as punishers within the same dose range, depending on the context of environmental conditions. Systematic evaluation of the environmental conditions which determine the type and direction of behavioral effects with a variety of drugs may have practical implications for the control of licit or illicit drug use by humans. Initial studies in this project demonstrated that nicotine can function either as a reinforcer to maintain behavior, or as a punisher (aversive or noxious stimulus) to suppress behavior, depending on the context in which is administered. It was the object of this project to extend these studies to include additional drugs under a variety of conditions.

In the initial studies, previous effects with histamine and nicotine were replicated using procedures which were modifications of ones used previously. In subsequent studies a variety of drugs was examined. Punishing effects were found for: ethyl-B-carboline-3-carboxylate, buspirone, gepirone, yohimbine, and quipazine. Drugs that appear to lack specific punishing effects under this procedure are cocaine and midazolam.



### Suppression of Behavior by Drug Injection

Subsequent studies have been examining the punishing effects of B-CCE in more detail. These studies have shown that flumazenil antagonizes the punishing effects of B-CCE, and that the antagonism is dose-related. The functions that have been collected at this point will allow an apparent pA analysis of the effect. This will provide information that may be of use in determining the receptor mechanism by which these drugs are exerting their behavioral effects.

Studies also have concentrated on the punishing effects of quipazine. While the punishing effects of B-CCE have been antagonized by the benzodiazepine receptor antagonist, flumazenil, this drug did not antagonize the punishing effects of quipazine. Currently, ongoing studies are concentrating on the antagonism of the punishing effects of quipazine by the 5-HT<sub>2</sub> antagonist, ketanserin.

### Publications

Katz, J.L., Takada, K., Barrett, J.E. and Cook, J.M.: Punishment of schedule-controlled responding with quipazine and B-carboline-3-carboxylic acid ethyl ester in squirrel monkeys. Presented at Behav. Pharmacol. Soc. Mtg., 1988.

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Prada, J.A., Takada, K., Katz, J.L., Goldberg, S.R. and Barrett, J.E.: Punishment of behavior with buspirone and gepirone in the squirrel monkey. Fed. Proc. 46: 1300, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00003-04 BPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: S.R. Goldberg Chief BPL, ARC, NIDA		
Others: J.L. Katz Research Psychologist BPL, ARC, NIDA		
J.A. Prada Research Psychologist BPL, ARC, NIDA		
M. Swedberg Foreign Fellow BPL, ARC, NIDA		
C.W. Schindler Staff Fellow BPL, ARC, NIDA		
COOPERATING UNITS (if any) None		
LAB/BRANCH Preclinical Pharmacology Branch		
SECTION Behavioral Pharmacology Laboratory		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 1.45	PROFESSIONAL: 1.15	OTHER: 0.30
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  General information on the behavioral pharmacology of a drug in a pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher as well as to establish a profile of behavioral effects. Multiple schedules of food presentation with both fixed-interval and fixed-ratio components have been most frequently used in this type of study since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. Second-order schedules of food presentation are useful for comparative studies of behavior maintained by food presentation or intravenous drug injection and may provide a particularly sensitive baseline for analyzing the rate-increasing effects of psychomotor stimulants such as cocaine. The present project involves the assessment of both the acute and chronic effects of a variety of drugs under multiple or second-order schedules of food presentation in squirrel monkeys and rats. The drugs studied include psychomotor stimulants, such as cocaine, various cocaine analogs, nicotine, various nicotine metabolites and its analogs, and caffeine. Since the behavioral effects of certain drugs depend on the type of event that maintains behavior, the effects of drugs are also studied on comparable performances maintained under fixed-interval schedules by either delivery of electric shock or by termination of a stimulus associated		

## Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals

with electric shock. Finally, the discriminative stimulus effects of selected drugs, such as nicotine and cocaine, are explored with a focus on the actions of their metabolites and analogs. These procedures provide stable, long-term sensitive baselines for quantitative assessment of both stimulant and depressant drug effects. The long-term nature of these baselines also makes them ideal for studying tolerance and cross-tolerance development to chronic treatment with various drugs, including cocaine, caffeine, adenosine analogs, and benzodiazepines for studying the mechanisms of action through pharmacological interaction with specific agonists and antagonists, and for studying the effects on behavior of various combinations of psychoactive drugs.

## Publications

Goldberg, S.R., Risner, M.E., Stolerman, I.P. and Reaville, C.: Nicotine and some related compounds: Effects on schedule-controlled behavior and discriminative properties in rats. Psychopharmacology, 1988, In press.

Katz, J.L.: Effects of drugs on stimulus control of behavior. III. Analysis of effects of pentobarbital and d-amphetamine. J. Pharmacol. Exp. Ther. 246: 76-83.

Katz, J.L. and Carney, J.M.: Progress in understanding the relationship between the adenosine receptor system and actions of methylxanthines. Pharmacol. Biochem. Behav. 29: 409, 1988.

Katz, J.L., Prada, J.A. and Goldberg, S.R.: Effects of adenosine analogs alone and in combination with caffeine in the squirrel monkey. Pharmacol. Biochem. Behav. 29: 429-432, 1988.

Risner, M.E., Cone, E.J., Benowitz, N.L. and Jacob, P: Effects of the stereoisomers of nicotine and normicotine on schedule-controlled responding and physiological parameters of dogs. J. Pharmacol. Exp. Ther. 244: 807-813, 1988.

Shannon, H.E., Hagen, T.J., Guzman, F. and Cook, J.A.: B-Carbolines as antagonists of the discriminative stimulus effects of diazepam in rats. J. Pharmacol. Exp. Ther. 246: 275-281, 1988.

Takada, K., Hagen, T.J., Cook, J.M., Goldberg, S.R. and Katz, J.L.: Discriminative stimulus effects of intravenous nicotine in squirrel monkeys. Pharmacol. Biochem. Behav. 30: 243-248.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA00004-04 BPL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Comparative Studies of Drug Self-Administration in Squirrel Monkeys and Humans

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	S.R. Goldberg	Chief	BPL, ARC, NIDA
Others:	J.E. Henningfield	Chief, BDL	BDL, ARC, NIDA
	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
	C.W. Schindler	Staff Fellow	BPL, ARC, NIDA
	R. Lamb	Staff Fellow	BDL, ARC, NIDA
	S. Heishman	Staff Fellow	BDL, ARC, NIDA

## COOPERATING UNITS (if any)

Biology of Dependence Laboratory, Clinical Biology Branch

## LAB/BRANCH

Preclinical Pharmacology Branch

## SECTION

Behavioral Pharmacology Laboratory

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.45

## PROFESSIONAL:

0.45

## OTHER:

0.00

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Self-administration studies permit an assessment of the relative contribution of environmental and pharmacologic factors to the self-administration of drugs, and to changes in the response to drugs due to tolerance and sensitization. Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine, morphine and nicotine under similar behavioral schedules and experimental conditions provide a means by which to assess the generality of biological variables influencing drug self-administration. These studies provide an opportunity for evaluating the role of environmental variables and the role of conditioning in human drug taking behavior and whether those roles differ from the roles of those variables in animal models of drug taking. Moreover, these investigations have shown that responding is maintained in human subjects in the same manner in which it is maintained in non-human experimental subjects. Additionally, behavior in humans and squirrel monkeys appears to be a function of similar variables. The stimuli that are associated with injections of cocaine develop conditioned reinforcing effects in humans in a manner similar to the manner in which these effects develop in squirrel monkeys. In humans, reinforcing effects of cocaine, morphine and nicotine can be detected at doses that do not occasion subjective reports of drug effects or drug liking. These results indicate that reinforcing effects of drugs can occur without traditional indications of abuse liability.

Comparative Studies of Drug Self-Administration in Squirrel Monkeys and Humans

Publications

Goldberg, S.R.: Effects of environmental stimuli associated with drug injections on persistent drug-seeking behavior: Second-order schedules. Pharmacol. Biochem. Behav. 29: 653-659, 1988.

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Katz, J.L.: Drugs as Reinforcers: Pharmacological and Behavioral Factors. In Lieberman, J.M. and Cooper, S.J. (Eds.): The Neuropharmacological Basis of Reward. Oxford, UK, Oxford University Press, 1988, In press.

Katz, J.L. and Goldberg, S.R.: Second-order Schedules of Drug Injection: Implications for Understanding the Reinforcing Effects of Drugs of Abuse. In Mellow, N.K. (Ed.): Advances in Substance Abuse. Greenwich, CT, JAI Press, Inc., 1988.

Ritz, M.C., Lamb, R.J., Goldberg, S.R. and Kuhar, M.J.: Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237: 1219-1223, 1987.

Swedberg, M.D.B., Henningfield, J.E. and Goldberg, S.R.: Evidence of Nicotine Dependency from Animal Studies: Self-Administration, Tolerance and Withdrawal. In Russell, M.A.H., Stolerman, I.P. and Wannacot, S. (Eds.): Oxford, UK, Oxford University Press, Oxford, 1988, In press.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-03 BPL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less, Title must fit on one line between the borders.)

Drug Effects on Classical Conditioning in Rabbits

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: S.R. Goldberg Branch Chief BPL, ARC, NIDA

Others: C.W. Schindler Staff Fellow BPL, ARC, NIDA

## COOPERATING UNITS (if any)

Department of Psychology, The University of Iowa, Iowa City, IA (J.A. Harvey)  
Department of Psychology, The American University, Washington, DC (S.J. Weiss)

## LAB/BRANCH

Preclinical Pharmacology Branch

## SECTION

Behavioral Pharmacology Laboratory

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.20

## PROFESSIONAL:

0.20

## OTHER:

00.00

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is being terminated as of September 30, 1988 and work being performed under this project will be incorporated into Z01 DA 00006-04, "Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists, and Other...".

The purpose of this project was to determine the effects of abused drugs on the acquisition of classically conditioned responses and to relate those effects to both behavioral and physiological processes. It was found that LSD enhances the acquisition of classically conditioned responses in the rabbit. This enhancement may be due to an increase in the reflex facilitation produced by LSD on the nictitating membrane response. In addition, the conditioning process itself was found to lead to an increase in the metabolic activity of the cochlear nucleus, possibly indicating that this structure is an important anatomical locus for the neuroanatomical plasticity important to learning. A second purpose was to determine how various conditioned or discriminative stimuli may interact when presented in combination.



### Drug Effects on Classical Conditioning in Rabbits

When discriminative stimuli are compounded, if the same maintaining event is used in each, additive summation results. This was shown to be true when water reinforcement maintains responding in one stimulus and food reinforcement in the other. However, if shock avoidance maintains responding during one stimulus and food reinforcement in the other, additive summation does not result. This procedure may be of great utility in determining the interaction of various motivational states.

### Publications

Schindler, C.W., Gormezano, I. and Harvey, J.A.: Effects of morphine ethylketocyclazocine, U-50,488H and naloxone on the acquisition of a classically conditioned response in the rabbit. J. Pharmacol. Exp. Ther. 243: 1010-1017, 1987.

Harvey, J.A., Winsky, L., Schindler, C.W., McMaster, S.E. and Welsh, J.P.: Asymmetric uptake of 2-deoxy-D-[<sup>14</sup>C] glucose in the dorsal cochlear nucleus during Pavlovian conditioning in the rabbit. Brain Res. 449: 213-224, 1988.

Harvey, J.A., Gormezano, I., Cool-Hauser, V.A. and Schindler, C.W.: Effects of LSD on classical conditioning as a function of CS-UCS interval: Relationship to reflex facilitation. Pharmacol. Biochem. Behav. 30: 433-441, 1988.

Weiss, S.J., Schindler, C.W., and Eason, R.: The integration of habits maintained by food and water reinforcement through stimulus compounding. J. Exp. Anal. Behav., In press.

Schindler, C.W. and Harvey, J.A.: The use of classical conditioning procedures in behavioral pharmacology. Drug Develop. Res., In press.

Weiss, S.J. and Schindler, C.W.: Integrating control generated by positive and negative reinforcement: Appetitive-aversive interactions. Animal Learning and Behavior, In press.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00006-04 BPL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists and

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C.W. Schindler

Staff Fellow

BPL, ARC, NIDA

Others: S.R. Goldberg

Chief

BPL, ARC, NIDA

J.L. Katz

Research Psychologist

BPL, ARC, NIDA

## COOPERATING UNITS (if any)

None

## LAB/BRANCH

Preclinical Pharmacology Branch

## SECTION

Behavioral Pharmacology Laboratory

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.10

## PROFESSIONAL:

0.80

## OTHER:

0.30

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is directed toward determining the various effects opioid agonists, antagonists, and mixed agonist-antagonists have on behavior including the ability to modify opioid self-administration. The effects of naltrexone are assessed in monkeys responding under second order schedules of intravenous morphine injection, in which each 30th response produces a visual stimulus and the first sequence of 30 responses completed after the lapse of a 1-hour period of time produces the stimulus and an injection of drug. Under this schedule, a relatively long sequence of responses can be maintained by infrequent injections and the effects of pharmacological pretreatments can be assessed without the potential confounds of direct interaction with the maintaining drug event. The direct behavioral effects of the opioids are assessed on schedule-controlled behavior maintained by food presentation, the acquisition of classically conditioned responses, and locomotor activity. The comparison of the drug effects in these various procedures permits a determination of whether there is a separation of the opioids across their behavioral and reinforcing effects.

**Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists and Other...**

The effects of naltrexone on the second-order schedule of morphine injection have been equivocal. One animal displayed profound sensitivity to naltrexone. Initially the behavior of this monkey was not disrupted by doses of naltrexone up to 3.0 mg/kg, but with repeated injection, doses as low as 0.03 mg/kg disrupted behavior. Other subjects did not show consistent effects with naltrexone. For subjects maintained by food presentation, only the highest dose of naltrexone (10.0 mg/kg) produced disruption. A clear separation of the effects of opioids was found on the acquisition of classically conditioned responses and their effects on locomotor activity. Moreover, naltrexone was found to produce clear behavioral supersensitivity when its effects are determined on schedule-controlled behavior in rats.

**Publications**

Harvey, J.A., Schindler, C.W. and Schreurs, B.G.: [d-Ala<sup>2</sup>]-leucine enkephalinamide: Evidence for a role of enkephalins in learning. Neuroscience 22 (Suppl.): 1514T, 1987.

Schindler, C.W., Gormezano, I. and Harvey, J.A.: Effects of morphine ethylketocyclozine, U-50,488H and naloxone on the acquisition of a classically-conditioned response in the rabbit. J. Pharmacol. Exp. Ther. 233: 1010-1017, 1987.

Schindler, C.W., Katz, J.L. and Goldberg, S.R.: Behavioral sensitivity to naltrexone in rats following acute injections. J. FASEB 2: A1567, 1988.

Schindler, C.W., Katz, J.L., and Goldberg, S.R.: The use of second-order schedules to study the influence of environmental stimuli on drug-seeking behavior. 10: Learning factors in substance abuse. In Ray, B. (Ed.): Learning Factors in Substance Abuse, NIDA Research Monograph, No. 84, Washington, DC, US Government Printing Office, 1988, pp. 180-195.

Solomon, R.E., Goodrich, J.E., and Katz, J.L.: Opioid receptor subtype-specific cross tolerance to the effects of morphine on schedule-controlled behavior in mice. Psychopharmacology, 1988, In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00007-04 BGL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Abuse Liability and Behavioral Effects of Benzodiazepines</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.L. Katz	Research Psychologist BPL, ARC, NIDA
Others:	J.M. Witkin	Senior Staff Fellow BPL, ARC, NIDA
	J.W. Griffiths	Visiting Fellow BPL, ARC, NIDA
	D. Spear	Staff Fellow BPL, ARC, NIDA
	J.A. Prada	Research Psychologist BPL, ARC, NIDA
COOPERATING UNITS (if any) Department of Chemistry, University of Milwaukee at Madison (J.M. Cook)		
LAB/BRANCH Preclinical Pharmacology Branch		
SECTION Behavioral Pharmacology Laboratory		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	1.35	0.40
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Benzodiazepines are among the most widely prescribed drugs. The widespread use of these compounds leads to concerns about their possible abuse. The present studies are designed to provide a characterization of the possible conditions that promote benzodiazepine abuse as well as information relevant to mechanisms of benzodiazepine action and dependence. The receptor specificity of the effects of benzodiazepines will be addressed by a $pa_2$ analysis of the various actions of benzodiazepines including ataxic, anxiolytic, and anticonvulsant effects. These actions will be assessed using standard behavioral tests. The specificity of the dependence produced by benzodiazepines will be examined in studies involving the precipitation of withdrawal by antagonists with differing specificity for subtypes of benzodiazepine receptors. In addition, the behavioral significance of the benzodiazepine system will be evaluated in studies using benzodiazepine receptor inverse agonists. The anxiogenic actions of these compounds are being assessed in studies of discrimination as well as studies of the aversive effects of anxiogenic agents. Finally, studies will analyze the withdrawal reaction to benzodiazepines to determine possible pharmacological treatment strategies for the management of the withdrawal reaction.		

**Abuse Liability and Behavioral Effects of Benzodiazepines**

**Publications**

Woods, J. H., Katz, J.L. and Winger, G.: Abuse liability of benzodiazepine. Pharmacol. Rev. 39: 251-413, 1987.

Witkin, J.M., Mansbach, R.S., Barrett, J.E., Bolger, G.T., Skolnick, P. and Weissman, B.A.: Behavioral studies with anxiolytic drugs: IV. Serotonergic involvement in the effects of buspirone on punished behavior of pigeons. J. Pharmacol. Exp. Ther., 243: 970-977, 1987.

Witkin, J.M., Lee, M.A. and Walczak, D.D.: Anxiolytic properties of amygdaloid kindling unrelated to benzodiazepine receptors. Psychopharmacology, In press.

Mansbach, R.S., Harrod, C., Hoffman, S.M., Nader, M.A., Lei, Z., Witkin, J.E. and Barrett, J.E.: Behavioral studies with anxiolytic drugs: V. Behavioral and in vivo neurochemical analyses in pigeons of drugs that increase punished responding. J. Pharmacol. Exp. Ther., 246: 114-120, 1988.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA00008-04 BPL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line, between the borders.)

Behavioral Pharmacology of Non-Opioid Analgesics

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: S.R. Goldberg

Branch Chief

BPL, ARC, NIDA

Others: M. Swedberg

Staff Fellow

BPL, ARC, NIDA

## COOPERATING UNITS (if any)

B. Nickel, Research Associate, Degussa Pharma, Frankfurt, FRG

## LAB/BRANCH

Preclinical Pharmacology Branch

## SECTION

Behavioral Pharmacology Laboratory

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.70

## PROFESSIONAL:

0.60

## OTHER:

0.10

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is being terminated as of September 30, 1988, with certain of its findings being pursued as related questions in Projects Z01 DA00006-04, "Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists and Other...", and Z01 DA00003-04, "Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals". The pharmacological mechanisms of action of potential non-narcotic analgesic compounds have been studied using a drug discrimination paradigm, a behavioral procedure which has evolved to become a major in vivo behavioral assay in pharmacology due to its demonstrated sensitivity in differentiating among drugs from different pharmacological classes. Operant rat chambers, enclosed in light- and sound-attenuating, fan ventilated enclosures, are used. The chambers are equipped with two response levers, a bright white house-light and a dim red light. Scrambled electric shocks can be delivered to the grid floor of the chamber by a constant current shock generator. Rats are trained under a fixed-ratio 5 (FR 5) schedule of stimulus shock termination to respond on one lever after an intraperitoneal injection of promising non-narcotic analgesic compounds and on the other lever after no-drug treatment.



### Behavioral Pharmacology of Non-Opioid Analgesics

In a series of discrimination studies completed this year, rats were trained to discriminate intraperitoneal injections of either flupirtine (10.0 mg/kg) or D-16949 (2.0 mg/kg), non-opioid analgesics in clinical use or in trials in Europe. Avoidance of electric shocks was contingent upon whether or not the training drug had been injected prior to the session. Putative agonists were substituted for the training drug, and putative antagonists were administered in combination with the training drug, respectively. The results indicate alpha-2 adrenergic mechanisms to be of primary importance in mediating the discriminative effects of flupirtine. Opiate mechanisms have been eliminated on the basis of non-substitutability of opioid analgesics and lack of effect of the opiate antagonist, naltrexone. With D-16949, tests with opioid analgesics, phencyclidine, d-amphetamine and LSD indicate lack of similarities in discriminative effects. Tests with serotonergic agonists and antagonists indicate that 5-HT<sup>1B</sup> mechanisms probably are of primary importance for mediating the discriminative effects of D-16949.

### Publications

Katz, J.L. and Goldberg, S.R.: Preclinical assessment of abuse liability of drugs. Agents and Actions 23: 18-26, 1988.

Swedberg, M.D.B., Shannon, H.E., Nickel, B. and Goldberg, S.R.: Pharmacological mechanisms of action of flupirtine: A novel centrally acting non-opioid analgesic evaluation by its discriminative effects in the rat. J. Pharmacol. Exp., 1988, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00009-02 BPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Cardiovascular Changes Induced by Cocaine in Squirrel Monkeys</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: S.R. Goldberg  Others: C.W. Schindler S.T. Rao	Branch Chief  Staff Fellow Foreign Fellow	BPL, ARC, NIDA  BPL, ARC, NIDA BPL, ARC, NIDA
COOPERATING UNITS (if any)  None		
LAB/BRANCH Preclinical Pharmacology Branch		
SECTION Behavioral Pharmacology Laboratory		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 1.25	PROFESSIONAL: 1.05	OTHER: 0.20
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>The effects of cocaine on a number of physiological parameters are being studied in the squirrel monkey. Monkeys are prepared with both venous and arterial catheters prior to the beginning of the experiment. During experimental sessions, the animals are seated in a standard squirrel monkey chair and connected to a blood pressure transducer via the arterial catheter. The venous catheter is connected to a syringe outside an acoustical chamber through which drugs can be administered.</p> <p>When cocaine is administered alone, there is a dose-dependent increase in arterial blood pressure. Higher doses of cocaine (0.3-3.0 mg/kg) produce decreases in heart rate in all the monkeys tested; however, lower doses (0.03 mg/kg) either have little effect or tend to increase heart rate. The decreases in heart rate observed at the higher doses is followed by increases in heart rate above saline baseline 20-30 minutes following cocaine injection. When cocaine injections were followed by either the calcium channel modulator, nimodipine, or the calcium channel entry blocker, verapamil, the blood pressure effect of cocaine was reversed. However, only verapamil reversed the heart rate effect of cocaine. Haloperidol (0.01-0.03 mg/kg) also appears to antagonize some of the effects of cocaine on cardiovascular function, but not as dramatically as the calcium channel antagonists.</p>		

**Publications**

Schindler, C.W., Katz, J.L., Goldberg, S. R., Nemeth-Coslett, R. and Henningfield, J.: Reinforcing and cardiovascular effects of cocaine in squirrel monkeys and humans. Pharmacol. Biochem. Behav. 30: 554-555, 1988.

Nahas, G.G., Trouve, R., Manger, W., Vinyard, C. and Goldberg, S.R.: Cocaine et toxicite des neurotransmetteurs endogenes. Acad. Natl. Med. Bull. 171: 669-673, 1987.

Trouve, R., Nahas, G.G., Vinyard, C. and Goldberg, S.R.: Cocaine and cardiovascular changes in the squirrel monkey. Proc. Soc. Exp. Biol. Med., 1988, In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00010-01 BPL
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Behavioral Pharmacology and Toxicology of Psychomotor Stimulants
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.M. Witkin	Staff Fellow
		BPL, ARC, NIDA
Others:	S.R. Goldberg	Chief
	J.L. Katz	Research Psychologist
	C.W. Schindler	Staff Fellow
		BPL, ARC, NIDA
		BPL, ARC, NIDA

COOPERATING UNITS (if any)
None

LAB/BRANCH Preclinical Pharmacology Branch
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SECTION Behavioral Pharmacology
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
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TOTAL MAN-YEARS: 1.85	PROFESSIONAL: 1.25	OTHER: 0.60
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CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input checked="" type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
<p>Behavioral effects of psychomotor stimulants are evaluated to characterize the complex and diverse pharmacology of these compounds as well as the range of behavioral and toxic actions which accompany acute and prolonged administration by different routes in rodents and primates. Compounds currently under investigation include cocaine and cocaine analogs, methamphetamine, d-amphetamine, and N,N-dimethylamphetamine. Experiments with these drugs are integrated with other ongoing work in the Branch on self-administration, physiological actions, genetic factors, and methoxylated amphetamines. A gamut of behaviors are studied including psychomotor stimulation or depression, behaviors controlled by different events, and discriminative stimulus effects. Evaluation of pharmacological means for altering behavioral and toxic effects of cocaine and related compounds is a key research problem in this work. Focus is currently on dopaminergic drugs, muscarinic agents, and calcium channel antagonists.</p>

## Behavioral Pharmacology and Toxicology of Psychomotor Stimulants

Coordinated experiments are conducted to delineate the neuropharmacological mechanisms of action of psychomotor stimulants. The behavioral and neurobiological consequences of chronic administration also comprise a large part of this project area. Emphasis is given to assessing the determinants of behavioral and neuropharmacological actions of repeated drug exposures and cessation of chronic drug administration. Information on tolerance, cross tolerance relationships, sensitization, and withdrawal should be generated from this project. As a whole, this research program is directed toward clinical application in the areas of assessment of the use of and neurobehavioral compromise from psychomotor stimulant abuse as well as the treatment or prevention of behavioral and neurobiological alterations resulting from this growing health problem. This is a new project.

## Publications

Witkin, J.M.: Non-Muscarinic Behavioral Neurotoxicity of Oxotremorine. In Dowdall, M.J. and Hawthorne, J.N. (Eds.): Cellular and Molecular Basis of Cholinergic Function, Chichester, England, Ellis Horwood, 1987, pp. 800-813.

Witkin, J.M., Alvarado-Garcia, R., Lee, M.A. and Witkin, K.M.: Nonmuscarinic neurotoxicity of oxotremorine. J. Pharmacol. Exp. Ther. 241: 34-41, 1987.

Witkin, J.M., Gordon, R.K. and Chiang, P.K.: Comparison of in vitro actions with behavioral effects of antimuscarinic agents. J. Pharmacol. Exp. Ther. 242: 796-803, 1987.

Witkin, J.M.: Behavioral Pharmacology of Compounds Affecting Muscarinic Cholinergic Receptors. In Thompson, T., Dews, P.B. and Barrett, J.E. (Eds.): Advances in Behavioral Pharmacology, Vol. 7, Hillsdale, NJ, Lawrence Erlbaum, In press.

Katz, J.L., Dworkin, S., Dykstra, L.A., Carter, R.B. and Witkin, J.M.: Some behavioral effects of repeated d-amphetamine administration. Drug Develop. Res., In press.

Witkin, J.M.: Central and peripheral muscarinic actions of physostigmine and oxotremorine on avoidance behavior of squirrel monkeys. Psychopharmacology, In press.

Witkin, J.M.: Alvarado-Garcia, R., Perez, L.A. and Witkin, J.M.: Central oxotremorine antagonist properties of pirenzepine. Life Sci. 42: 2467-2473, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00011-01 BPL
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PERIOD COVERED  
October 1, 1987 to December 31 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Behavioral and Neurotoxic Effects of Substituted Amphetamines

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
Others:	J.M. Witkin	Senior Staff Fellow	BPL, ARC, NIDA
	E. Shores	Research Psychologist	BPL, ARC, NIDA

COOPERATING UNITS (if any)  
Department of Neurology, The Johns Hopkins University School of Medicine  
(G.A. Ricaurte)

LAB/BRANCH  
Preclinical Pharmacology Branch

SECTION  
Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 1.75	PROFESSIONAL: 1.35	OTHER: 0.40
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CHECK APPROPRIATE BOX(ES)  
☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The present studies are designed to examine behavioral and neurotoxic effects of substituted amphetamines. The abuse potential of these compounds is studied by assessing the reinforcing effects of these drugs when delivered intravenously to subjects trained to self-administer cocaine. Various substituted amphetamines, as well as other reference drugs of abuse, will be studied for their reinforcing effects under fixed-ratio schedules of drug injection. The psychomotor stimulant effects of these compounds will be examined in squirrel monkeys, rats, and pigeons trained to respond under fixed-interval schedules of reinforcement. Stable performance under these schedules will be examined after administration of the various substituted amphetamines as well as reference compounds. In some studies, the neurotoxic effects of these compounds will be assessed using standard techniques. In addition, studies of the effects of drugs active on serotonergic systems, before and after long-term treatment with (+)-3,4-methylenedioxymethamphetamine (MDMA), will better define the duration of the neurotoxic effects of MDMA in the primate and will aid in the development of functional correlates of MDMA-induced neurotoxicity.

This is a new project; no publications.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00001-03 BGL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Pharmacogenetics: Acute Responses to Drug Administration		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	F.R. George	Staff Fellow BPL, ARC, NIDA
Others:	S.R. Goldberg	Chief BPL, ARC, NIDA
COOPERATING UNITS (if any)  None		
LAB/BRANCH Preclinical Pharmacology Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.85	0.55	1.30
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>With the exception of ethanol, genetic factors have not been widely examined with other abused substances. However, existing reports do indicate large genetic differences in both acute sensitivity and predisposition to self-administer drugs, particularly narcotics. In the present project, the acute behavioral effects of drug administration are being systematically explored in rats and mice. Drugs studied include opiate agonists, stimulants, particularly cocaine, benzodiazepines, barbiturates, and phencyclidine. A variety of behavioral tasks, including open field activity, rotational behavior, tail flick, sleep time, rotorod stability, and tilt-plane coordination are used, as well as simple physiological measures such as body temperature, blood pressure, heart rate and respiration rate. For each drug tested, dose-response patterns are obtained across a wide range of drug effects. Several inbred strains of mice and/or rats are included to determine an estimate of the genetic variation for each behavior or physiological measure. Where appropriate, these measures will be correlated with each other to estimate the commonality among the responses studied. In all these studies, genotype will be incorporated as an independent variable. As the initial strain studies are completed, further genetic designs, such as Mendelian analysis, are being initiated to obtain estimates of the number of loci involved in determining a particular trait as well as its mode of transmission. Where appropriate, additional biochemical studies are implemented to aid in determining the neural sites of action. Recent findings include: (1) An anomalous seizure response to cocaine; (2) A genetically determined depressant effect of cocaine; and (3) A mouse genotype insensitive to cocaine.</p>		

Pharmacogenetics: Acute Responses to Drug Administration

Publications

George, F.R. and Goldberg, S.R.: Genetic factors in response to cocaine. Mechanisms of Cocaine Abuse and Toxicity. National Institute on Drug Abuse Monograph, 1988, In press.

George, F.R., Elmer, G.I., Meisch, R.A. and Goldberg, S.R.: Oral self-administration of cocaine in C57BL/6J mice and the relationship between intake and behavioral effects. J. Pharmacol. Exp. Ther. 1989, In press.

George, F.R., Ritz, M.C. and Meisch, R.A.: The effects of ethanol on schedule-controlled responding in AA and ANA rats. Psychopharmacology, 1989, In press.

Suzuki, T., Koike, Y., Yanaura, S., George, F.R. and Meisch, R.A.: Genetic differences in the development of physical dependence on pentobarbital in four inbred strains of rats. Jpn. J. Pharmacol. 45: 479-486, 1987.

George, F.R.: The role of arachidonic acid metabolites in mediating ethanol self-administration and intoxication. Ann. NY Acad. Sci., 1988, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00002-03 BGL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Pharmacogenetic Factors in Drug Reinforced Behavior		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	F.R. George	Staff Fellow
		BGL, ARC, NIDA
Others:	S.R. Goldberg	Chief
		BPL, ARC, NIDA
COOPERATING UNITS (if any) None		
LAB/BRANCH Preclinical Pharmacology Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	0.55	1.20
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>             The objectives of the proposed research are to identify and study factors that control drug reinforced behavior using genetically divergent rat and mouse populations. The methodology and principles of operant conditioning and pharmacogenetic analysis will be used. The studies will be limited to conditions in which the drug is taken orally and functions as a positive reinforcer. The focus will be on variables that control drug reinforced behaviors, especially genetic variables, but also including pharmacological variables and environmental variables, e.g., drug concentration and fixed ratio size. Emphasis will be given to systematically studying variables over a range of variables; interactions among variables will be parametrically explored. The proposed studies are important because (1) drug intake will be examined under conditions in which it is taken orally and functions as a reinforcer; (2) they will explore genetic and environmental factors and their interactions which contribute to drug self-administration; and (3) the use of genetically defined animals will provide information concerning the degree to which genetic factors regulate drug-seeking behavior and will contribute to a systematized body of knowledge that will aid in the analysis of the complex problems of drug abuse. Recent findings include: (1) Defining the existence of genetic differences in reinforcement from cocaine; and (2) Defining genetic differences in reinforcement from opiates.           </p>		



Pharmacogenetic Factors in Drug Reinforced Behavior

Publications

Meisch, R.A. and George, F.R.: Influence of genetic factors on drug reinforced behavior in animals. In Pickens, R. and Svikus, D. (Eds.): Biological Vulnerability to Drug Abuse, National Institute of Drug Abuse Monograph, 1988, In press.

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## Neuroscience Branch

Michael J. Kuhar, Ph.D., Chief

### Introduction

The Neuroscience Branch employs a multifaceted research strategy designed to elucidate the mechanisms of action of abused drugs and their effects on biological systems and to develop pharmacological modalities for intervention and treatment. Research areas include molecular genetics, drug receptor binding, cerebral metabolic mapping, electrophysiology and positron emission tomography (PET) scanning in humans.

The Branch underwent a reorganization in the past year, forming a new laboratory. It is now composed of three laboratories: the Molecular Pharmacology Laboratory, the Neuropharmacology Laboratory, and the Neurobiology Laboratory. The Neurobiology Laboratory evolved from the Neuropeptide Unit in the Molecular Pharmacology Laboratory. The Laboratories are subdivided into functional and collaborative units, sometimes with other laboratories.

### 1. Molecular Pharmacology Laboratory — Chief, Michael J. Kuhar, Ph.D.

#### Overview

The Molecular Pharmacology Laboratory focuses on the molecular mechanisms of action and the molecular effects of drugs of abuse. The composition and areas of research in the Laboratory have changed since last year because of the addition of another major investigator, Dr. George Uhl, in the area of molecular biology and because of the separation of a team headed by Dr. Errol DeSouza to form a new Laboratory, the Neurobiology Laboratory. At present, the major investigators in the Molecular Pharmacology Laboratory include Dr. Michael Kuhar, Dr. Mathew Lo, and Dr. George Uhl. Drs. Lo and Uhl are working in the general area of molecular biology of drugs of abuse, while Dr. Kuhar continues to focus on drug and neurotransmitter receptors and the effects of drugs of abuse. It is hoped that this diversity will insure that a broad interdisciplinary molecular approach is used in addressing drug abuse problems.

One area of emphasis in the Laboratory is the mechanism of action of cocaine. Dr. Kuhar and co-workers previously identified, in a series of drug receptor binding studies, a cocaine receptor that had pharmacological properties that correlated with drug self-administration in primates. This finding suggested that this particular cocaine binding site, which was the cocaine receptor on the dopamine transporter in dopaminergic nerve terminals, is the cocaine receptor responsible for the reinforcing properties of the drug and, therefore, the receptor that is related to the abuse of cocaine. This finding has led to an emphasis on the cocaine binding site and on the dopamine



transporter. Significant efforts are now being made to solubilize and purify the transporter, to characterize it using structure-activity-relationships, to identify new and more effective ligands for studying the transporter, and to define ligands and procedures by which the cocaine receptor on the transporter can be imaged in humans using PET scanning.

Related to the identification of a receptor for the psychomotor stimulant cocaine, efforts were also made to identify a receptor for amphetamine that could be correlated to its substance-abusing properties. However, after extensive efforts, no such amphetamine binding site or receptor has been found. Despite this, efforts continue and it is assumed that the properties of amphetamine are mediated by some specific molecular site that, in theory, could be identified in binding studies.

In addition to studies of the cocaine binding site, the binding of cocaine to other drug and neurotransmitter sites in brain has been examined. It was noted that cocaine binds to sigma receptors at pharmacologically relevant plasma concentrations. While the physiological significance and clinical relevance of the sigma receptor may be somewhat controversial, it is possible that activation of sigma receptors is related to psychotomimetic effects of opiates and various other drugs. Thus, it is reasonable to postulate that cocaine binding at the sigma receptor could be responsible for some of the psychotomimetic properties of cocaine.

Also, it was found that cocaine binds to muscarinic cholinergic receptors. However, the binding constants are high, suggesting that cocaine would bind to these receptors only at higher plasma concentrations than normally anticipated for pharmacological activity. In fact, plasma concentrations of cocaine in the 20 uM range are usually associated with toxic or lethal doses of the drug. Thus, cocaine could exhibit anticholinergic activity when it is present in high concentrations and it is conceivable that these anticholinergic properties of cocaine could contribute to the toxic effects of the drug.

Other drugs of abuse have been studied as well. Methylenedioxymethamphetamine (MDMA) is a methylated amphetamine derivative which is currently abused. Previous neurochemical studies had shown that closely related compounds, such as methylenedioxyamphetamine (MDA), were neurotoxic in the sense that they produced long-lasting depletions of serotonin in brain. Other amphetamine derivatives exhibited this property as well. Therefore, the potential of MDMA to cause a depletion of serotonin was assessed in neurochemical studies. The studies utilized a new approach for determining neuronal degeneration. Ligands binding to serotonin transporters were included in the neurochemical measurements. It was reasoned that since binding to a transporter required the presence of an intact nerve terminal, transporter binding levels would be reflective of relative levels (or losses) of serotonin-containing nerve terminals. A variety of previous studies had shown that the transporter molecules are not easily up- or down-regulated and, therefore, any decreases in transporter binding would be suggestive of a loss and degeneration of serotonin-

containing nerve terminals. It was subsequently shown that chronic administration of MDMA at higher doses, but nevertheless doses that could be achieved by humans in repeated administration situations, caused a long-lasting depletion of serotonin and also a reduction in the number of serotonin transporters in brain. This suggestion of a destruction of serotonin-containing nerve terminals by MDMA was confirmed by extensive immunocytochemical studies in which a swelling and degeneration of serotonin-containing axons were observed directly.

Another focus in the Laboratory involves the utilization of PET scanning techniques to study drug receptors as well as to examine the effects of drugs of abuse in humans. Since the reinforcing properties of cocaine have been associated with the dopamine system, imaging of several components of the dopaminergic system is of interest. N-methylspiperone is a useful ligand for binding to dopamine-2 (D2) receptors in vivo. Accordingly, extensive studies were carried out to characterize the binding of this ligand to dopamine receptors in in vitro studies. Also, an animal model of the in vivo binding of the drug to D2 dopamine receptors was produced using mice. It was shown that the drug binds to dopamine (and to a lesser extent serotonin-2) receptors in vivo in mouse brain as well as in human brain.

Other PET scanning studies of drug receptors focused on benzodiazepine receptors. Benzodiazepine receptors in brain have been previously imaged. It was found that co-administration of a variety of other drugs with benzodiazepine ligands can alter the extent of labeling and time course of labeling of benzodiazepine receptors in brain with radiolabeled ligand. The precise mechanism causing this effect is unknown. However, it is a relevant finding for PET scanning, since it shows that the addition of another drug to a biological system can alter the ligand binding of a drug to a receptor in an unpredictable way that could confuse interpretation of data generated using combinations of drugs. Thus, it is anticipated that ultimately these studies will result in more accurate interpretations of PET scanning data.

Another drug known to affect dopaminergic systems is N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is a highly neurotoxic substance of abuse that causes a degeneration of dopaminergic neurons in the brain. Since this drug seems to have a relatively preferential affinity for nigrostriatal neurons, it can produce Parkinson's disease. Notably, several individuals who have taken the drug extensively now have advanced stages of Parkinson's disease. Thus, a specific goal of research ongoing in the Laboratory has been directed toward attempting to identify the mechanisms by which MPTP produces this destruction.

While most studies in other laboratories have emphasized identifying biochemical changes caused by MPTP and the metabolites of MPTP, a novel approach was adopted which was directed toward identifying all of the components in cells which are required to produce the toxic effects of MPTP. PC12 cells were mutated by a retrovirus and selected for survival by adding an active metabolite of MPTP to media. The cells that survived were mutated by the virus and through the use of molecular biological techniques, it has been



possible to identify regions of the gene that contain the viral chromosome. These, by inference, are regions that contain genes that must be intact for MPTP to be toxic; therefore, one might conclude that these genes must be the ones that make proteins related to the toxicity of MPTP. Five distinct chromosomal regions in PC12 cells which are important for drug toxicity have been identified. Detailed examination of one particular region has led to the identification of two genes. Moreover, the cDNA's for these genes have been cloned. Analysis of their DNA sequences revealed a 60-80% homology with several known forms of the rat cytochrome P450 gene. This implies that metabolism of the drug within the cell may be essential for toxicity to occur. Current efforts are directed at identifying other gene targets, especially the catecholamine transporter, using the same strategy.

Other molecular biological studies are aimed at identifying genes for drug and neurotransmitter receptors and other proteins involved in the action of drugs of abuse. For example, some receptors for neurotransmitters have been cloned in other laboratories. Thus, two novel expression-cloning strategies for identifying genes related to neurotransmitter and drug receptor molecules are being developed. One involves the expression of drug receptors in oocytes and another involves the direct binding of radioligands to clones in order to identify specific clones expressing relevant drug receptors. There is also a focus on neuronal regulation of the expression of genes for neurotransmitters intimately involved with drugs of abuse. High resolution neuroanatomical approaches such as in situ hybridization are used. The effects of abused drugs on gene expression as well as effects of alterations in activities in defined neuronal circuits are being studied on neuronal expression.

#### Summary of Ongoing Research

##### A. The Cocaine Receptor: Kuhar, M.J., Ritz, M., Sharkey, J. and Lew, R.

Evidence has been presented in the past which indicates that the cocaine receptor related to drug self-administration is some part of the dopamine transporter. Hence, efforts are underway to characterize this transporter in detail. Current efforts include structure-activity studies, the use of various ligands to identify and study the transporter, solubilization and purification of the transporter, and localization of the transporter using imaging techniques.

##### B. Drug Receptors, Neurotransmitters and Addiction: Kuhar, M.J., Ritz, M., Sharkey, J. and Lew, R.

This multifaceted project is directed towards studying the interaction of drugs of abuse with brain neurochemicals. The goal of these studies is to elucidate the effects of drugs on the brain and to clarify their mechanisms of action. Current efforts include a



study of the neurotoxic effects of methylated amphetamines, an examination of the distribution of receptors in brain, an evaluation of the involvement of serotonin systems and receptors in drug self-administration, and an analysis of the interaction of various amphetamines with cocaine receptors and other drug receptors in brain. Emphasis has been placed on serotonin systems and drugs of abuse as well as on the mechanism of action of amphetamines.

**C. Measuring Drug Receptors In Vivo: Kuhar, M.J., Sharkey, J., Ritz, M. and Lew, R.**

While measuring and studying receptors in vitro is an established and routine approach, working with receptors in vivo is currently a complex frontier. Having identified a cocaine receptor in vitro that correlates with drug self-administration, attempts will be made to label the receptor preferentially in vivo with various ligands. Achievement of this goal will hopefully permit measurement of these receptors in vivo in humans using PET scanning.

**D. Genes Involved in MPTP Uptake and Neurotoxicity: Lo, M.M.S. and Kadan, M.J.**

Neurodegeneration induced by MPTP is mediated by several proteins, which include those involved in the process of uptake of the drug through the catecholamine transporter, and other, yet unidentified, intracellular proteins. These studies are aimed at identifying these proteins and cloning their genes. An enzyme has already been identified by genetically analyzing PC12 mutants which becomes resistant to MPTP. Current efforts include identifying other neuronal proteins (and their genes) which may be involved in the resulting drug toxicity observed, as well as characterizing these genes and their expression. Special emphasis has been placed on the catecholamine transporter gene.

**E. Receptor cDNA Expression Cloning: I. Ligand Autoradiographic Screening: Lo, M.M.S. and Kadan, M.J.**

Identifying genes encoding the cell surface receptors for abused drugs is an important step in the molecular biology of drug abuse. Since these rare membrane proteins are difficult to purify through conventional means, expression-cloning approaches are being developed to identify the genes encoding drug receptors. Current efforts include optimizing stepwise efficiency of a ligand autoradiographic screening procedure, increasing the rapidity and reliability of the procedure, and improving the libraries which can be screened for expression of neurotransmitter and drug receptors.

**F. Receptor cDNA Expression Cloning: II. Xenopus Oocyte Expression: Lo, M.M.S. and Kadan, M.J.**

A method for expression-cloning that complements the ligand autoradiographic approach utilizes the powerful expression system of the *Xenopus* oocyte. Current efforts include establishment of the system, validation of a means for monitoring expression of dopamine uptake cDNAs in this system, and establishment of libraries for "sib selection" of drug and neurotransmitter receptors. It is anticipated that this procedure, and the ligand autoradiographic screening, should allow direct cloning of receptor cDNAs without requiring purification of receptor protein.

**G. Neuronal Expression of Genes for Neurotransmitters Related to Drug Abuse: Lo, M.M.S. and Kadan, M.J.**

Understanding the ways in which individual neurons regulate their expression of neurotransmitters that are related to drug abuse may help to elucidate neurochemical mechanisms for drug action, including the development of tolerance and dependence. Using in situ hybridization and Northern blot analyses, changes have been detected in the neuronal expression of several neuropeptide genes in both animal and human tissues that may relate to drug action. The morphine-induced changes in preproenkephalin expression found in striatal neurons exhibit a time course consistent with a role for this agonist-induced down-regulation in opiate tolerance/dependence. Current efforts include extending this study to examine drug-induced changes in enkephalin gene expression in neurons in other parts of the nervous system, and to evaluate function-related changes in gene expression in areas of the brain implicated in drug-induced reinforcement processes such as the ventral tegmental area.

**Publications**

Battaglia, G., Yeh, S.Y., O'Hearn, E., Molliver, M.D., Kuhar, M.J. and DeSouza, E.B.: 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxamphetamine destroy serotonin terminals in rat brain: Quantification of neurodegeneration by measurement of <sup>3</sup>H-paroxetine-labeled serotonin uptake sites. J. Pharmacol. Exp. Ther. 242: 911-916, 1988.

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## Abstracts In Press

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Kadan, M.J. and Lo, M.M.S.: MPP<sup>+</sup>-resistant PC12 cells created by retroviral insertion. Neurosci. Abstr., 1988, In press.

## Abstracts In Press (Cont'd)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER <b>Z01 DA00106-03 MPL</b>
PERIOD COVERED <b>October 1, 1987 to December 31, 1987</b>		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>AIDS Related Research</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div style="width: 30%;"> <b>PI: M.M.S. Lo</b> </div> <div style="width: 65%;"> <b>Chief, Molecular Biology and Genetics Unit</b> </div> <div style="width: 30%;"> <b>MPL, ARC, NIDA</b> </div> </div>		
COOPERATING UNITS (if any) <b>None</b>		
LAB/BRANCH <b>Molecular Pharmacology Laboratory, Neuroscience Branch</b>		
SECTION <b>Molecular Biology and Genetics Unit</b>		
INSTITUTE AND LOCATION <b>Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224</b>		
TOTAL MAN-YEARS: <b>1.50</b>	PROFESSIONAL: <b>1.00</b>	OTHER: <b>0.50</b>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div style="width: 30%;"> <input type="checkbox"/> (a) Human subjects  <input type="checkbox"/> (a1) Minors  <input type="checkbox"/> (a2) Interviews         </div> <div style="width: 30%;"> <input type="checkbox"/> (b) Human tissues         </div> <div style="width: 35%;"> <input checked="" type="checkbox"/> (c) Neither         </div> </div>		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <div style="margin-top: 10px;"> <p>The aim of this Project was to produce monoclonal antibodies to the human immunodeficiency virus (HIV). Very high affinity antibodies are required for the purpose of vaccine development, and for direct HIV detection. Two sources of the HIV virus used were whole inactivated virus, and a genetically-engineered fusion protein containing a portion of the HIV gp 41 protein. Four fusions were performed and produced several antibodies. Many of these were directed to the p24 protein. One antibody showed extremely high immunoreactivity.</p> <p>This Project was terminated on December 31, 1987, in order to direct resources to another Project (Z01 DA00111 MBL); the work was continued as a collaboration with Dr. P.Y. Tsong at the Department of Biological Chemistry, Johns Hopkins University, School of Medicine. Except for technical consultation in this collaboration, no other NIDA resources have been expended on this Project.</p> </div>		

AIDS Related Research

Publications

Lo, M.M.S. and Tsong, T.Y.: Producing Monoclonal Antibodies by Electrofusion. In Newmann, E., Sowers, A. and Jordan, C. (Eds.): Electroporation and Electrofusion In Cell Biology. New York, NY, Plenum Press, 1988.

Tsong, T.Y., Tomita, M. and Lo, M.M.S.: Pre-Selection of B-Lymphocytes by Antigen for Fusion to Myeloma Cells by Pulsed Electric Field (PEF) Method. In Oki, S. et al. (Eds.): Molecular Mechanism of Membrane Fusion, New York, NY, Plenum Press, 1987.

Lo, M.M.S.: Producing monoclonal antibodies by electrofusion. IEEE, Engineering in Medicine and Biology Society Abstr. 9: 1987.

Conrad, M.K. and Lo, M.M.S.: Hybridoma Production Facilitated by Avidin-Biotin Mediated Cell Fusion. Methods in Enzymology, 1988, In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00107-03 MPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Measuring Drug Receptors <u>In Vivo</u>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	M.J. Kuhar	Chief, Neuroscience MPL, ARC, NIDA
Others:	M.C. Ritz	Staff Fellow MPL, ARC, NIDA
	N.E. Goeders	Associate Professor DNM, JHU
	H.N. Wagner	Director DNM, JHU
	D. Wong	Professor DNM, JHU
COOPERATING UNITS (if any) Louisiana State University, Department of Pharmacology & Johns Hopkins University, Division of Nuclear Medicine		
LAB/BRANCH Molecular Pharmacology Laboratory, Neuroscience Branch		
SECTION None		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 2.00	PROFESSIONAL: 1.25	OTHER: 0.75
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>           This project has advanced in several areas. One study characterized the binding of <sup>3</sup>H-N-methylspiperone to dopamine and serotonin receptors <u>in vivo</u>. While the drug has been used in PET scanning studies in humans, there had been no suitable animal model of the <u>in vivo</u> binding of the drug. It was shown that the drug binds to dopamine and serotonin receptors <u>in vivo</u> in mouse brain providing an animal model whereby the binding can be studied in a more extensive fashion than it can be in humans. These more extensive studies will help in understanding the significance of its localization in the human brain.         </p> <p>           It had previously been shown that a radiolabeled benzodiazepine drug can be used to label benzodiazepine receptors <u>in vivo</u>. In the current studies, it has been shown that co-administration of a variety of other drugs can alter the time course and magnitude of the labeling of benzodiazepine receptors <u>in vivo</u>. Sometimes these drugs are not related to the benzodiazepines, suggesting some complicated effect of drug on the penetration of the radiolabeled benzodiazepine into brain and its subsequent receptor labeling.         </p>		

## Measuring Drug Receptors In Vivo

These results provide an important caution for PET scanning studies of benzodiazepine receptors since they show that adding another drug to an animal can significantly alter the binding pattern of the radiolabeled drug to receptors. Since many PET scanning studies require the co-administration of more than one drug, this study is a beginning in understanding all of the complicated factors that may come into play in these situations. Ultimately, this will result in a more accurate interpretation of PET scanning data.

## Publications

Frost, J.J., Smith, A.C., Kuhar, M.J., Dannals, R.F. and Wagner, Jr., H.N.: In vivo binding of <sup>3</sup>H-N-Methylspiperone to dopamine and serotonin receptors. Life Sci. 40: 987-995, 1987.

Goeders, N.E., Ritz, M.C. and Kuhar, M.J.: Buspirone enhances benzodiazepine receptor binding in vivo. Neuropharmacol. 27: 275-280, 1988.

Kuhar, M.J. and Goeders, N.E.: Receptor Mapping in Psychopharmacology. In Meltzer, H.Y. (Ed.): Psychopharmacology: The Third Generation of Progress. New York, NY, Raven Press, 1987, pp. 313-316.

Kuhar, M.J.: Imaging receptors for drugs in neural tissue. Neuropharmacol. 26: 911-916, 1987.

Kuhar, M.J.: Human Brain Imaging. In Jones, E.G. (Ed.): Molecular Biology of the Human Brain. New York, NY, Alan R. Liss, Inc., 1988, pp. 185-190.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER <b>Z01 DA00108-03 MPL</b>
PERIOD COVERED <b>October 1, 1987 to December 31, 1988</b>		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>The Cocaine Receptor</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: <b>M.J. Kuhar</b>	<b>Chief</b>	<b>MPL, ARC, NIDA</b>
Others: <b>M.C. Ritz</b>		
<b>J. Sharkey</b>		
<b>R. Lew</b>		
<b>J.A. Schender</b>		
<b>R.C. Hanson</b>		
<b>Staff Fellow</b>		
<b>Visiting Fellow</b>		
<b>Visiting Fellow</b>		
<b>Researcher</b>		
<b>Researcher</b>		
<b>MPL, ARC, NIDA</b>		
<b>MPL, ARC, NIDA</b>		
<b>MPL, ARC, NIDA</b>		
<b>Nova Pharmaceuticals</b>		
<b>Nova Pharmaceuticals</b>		
COOPERATING UNITS (if any)		
<b>None</b>		
LAB/BRANCH		
<b>Molecular Pharmacology Laboratory, Neuroscience Branch</b>		
SECTION		
<b>None</b>		
INSTITUTE AND LOCATION		
<b>Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224</b>		
TOTAL MAN-YEARS: <b>2.00</b>	PROFESSIONAL: <b>1.25</b>	OTHER: <b>0.75</b>
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) Human subjects		
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		
<input type="checkbox"/> (b) Human tissues		
<input checked="" type="checkbox"/> (c) Neither		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
<p>In a series of drug binding studies, a cocaine receptor with pharmacological properties was identified that correlated with drug self-administration in primates. This suggests that this cocaine receptor, actually the cocaine binding site on the dopamine transporter, is the one of relevance to abuse of cocaine. Efforts are being made to solubilize and purify this dopamine transporter, and some progress has been made.</p> <p>The binding of cocaine has also been examined at other sites that are not directly related to its self-administration properties, but may be related to the other properties of cocaine. For example, it was found that cocaine binds to sigma receptors at relevant plasma concentrations. The pharmacological properties of the sigma receptor are such that it does not account for the self-administration of the drug but may be related to some of the psychomimetic properties of cocaine. Also, the binding of cocaine to muscarinic cholinergic receptors has been examined. It is possible that cocaine can interact with these receptors under physiological conditions but only at higher doses of cocaine. These higher doses, which may be toxic, suggest that cocaine's action at muscarinic cholinergic receptors may somehow contribute to its toxic properties.</p>		



The Cocaine Receptor

Publications

Sharkey, J., Glen, K.A., Wolfe, S. and Kuhar, M.J.: Cocaine binding at sigma receptors. Eur. J. Pharmacol. 149: 171-174, 1988.

Sharkey, J. and Kuhar, M.J.: <sup>3</sup>H-GBR 12935 labels the cocaine binding site associated with dopamine uptake inhibition. The Pharmacologist 29(3): 160, 1987.

Sharkey, J., Ritz, M.C., Schender, J.A., Hanson, R.C. and Kuhar, M.J.: Cocaine inhibits muscarinic cholinergic receptors in heart and brain. J. Pharmacol. Exp. Ther., 1988, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00110-03 MPL
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PERIOD COVERED  
October 1, 1987 to December 31, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Cloning of Genes Regulating the Human POMC Gene

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: M.M.S. Lo Chief, MPL, ARC, NIDA  
Molecular Biology & Genetics Unit

COOPERATING UNITS (if any)

None

LAB/BRANCH  
Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION  
Molecular Biology and Genetics Unit

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.40	PROFESSIONAL: 0.30	OTHER: 0.10
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CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project was terminated on December 31, 1987, so that more effort could be directed at another project (Z01 DA00111 MPL).

The purpose of this Project was to identify proteins which regulate the pro-opiomelanocortin (POMC) gene. Various fragments from the human POMC gene were subcloned and attached to bacterial proteins. Nuclear extracts from an anterior pituitary cell line (att20) protected small discrete POMC sequences from digestion with exonuclease. Nuclear extract from other cell lines did not protect the POMC DNA. This Project confirmed: 1) the existence of tissue specific nuclear proteins which recognized and bound to the POMC gene; and 2) specific DNA sequences which are involved in regulating this gene. This finding is important in studying how the POMC gene is regulated. Further work will be required to isolate the nuclear proteins, and the POMC DNA sequence.

No publications.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00111-03 MPL
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cloning of Genetic Sequences Involved in the Neurotoxicity of MPP+
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: M.M.S. Lo	Chief, Molecular Biol. & Genetics Unit	MPL, ARC, NIDA
Others: M.J. Kadan S.G. Carlson	Staff Fellow Research Assistant	MPL, ARC, NIDA MPL, ARC, NIDA

COOPERATING UNITS (if any) None
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LAB/BRANCH Molecular Pharmacology Laboratory, Neuroscience Branch
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SECTION Molecular Biology and Genetics Unit
--

INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
--

TOTAL MAN-YEARS: 5.50	PROFESSIONAL: 2.50	OTHER: 2.50
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CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input checked="" type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
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MPTP, a substance of abuse, is highly neurotoxic in humans, which often results in an illness resembling Parkinson's Disease. Toxicity is mediated by uptake of MPP+, the active metabolite of MPTP, into neurons. The precise mechanism of how MPP+ causes cell death can be studied in the rat PC12 cell line. PC12 cells have been infected with a recombinant retrovirus, and selected mutants with lethal doses of MPP+. It has been shown that a few regions of the PC12 genome (loci) suffered repeated retroviral integration. These regions are critical for MPP+ neurotoxicity, and presumably contain genes which become functionally inactivated after viral insertion. Recent progress has come from examining one of five frequently mutated loci. The genomic DNA from the mutated locus, and two distinct genes residing in this DNA, have been cloned. The cDNAs for these genes (named A and B) have been cloned from a PC12 cDNA library. Genes A and B are both specifically expressed in normal PC12 cells. The A gene was found to be induced by more than 20 fold following NGF treatment, whereas the B gene was unstimulated. Analysis of DNA sequence for two-thirds of the B gene revealed a 60% to 80% homology with several known forms of the rat cytochrome P450 gene.



**Cloning of Genetic Sequences Involved in the Neurotoxicity of MPP+**

These findings are significant because two specific components important in MPTP/MPP+ neurotoxicity were identified and their genes were cloned. In the next phase of this project, the other components involved in drug resistance will be identified. One key protein is the catecholamine uptake site. Identification and cloning of the genes for the uptake site will be critical in the study of cocaine abuse.

**Publications**

Lo, M.M.S., Dersch, C.M. and Mamalaki, C.: Retroviral infection in PC12 produces MPTP resistant mutants. Neurosci. Abstr. 13: 78, 1987.

Mamalaki, C., Douglas, R.C., Carlson, S.G., Dersch, C.M. and Lo, M.M.S.: DNA sequences in MPTP neurotoxicity. Neurosci. Abstr. 13: 558, 1987.

Lo, M.M.S., Conrad, M.K., Mamalaki, C. and Kadan, M.J.: Retroviral-mediated gene transfer: Applications in neurobiology. Mol. Neurobiol. 2: 1-29, 1988.

Kadan, M.J. and Lo, M.M.S.: MPP+ resistant PC12 cells created by retroviral insertion. Neurosci. Abstr., In press, 1988.

Lo, M.M.S., Kadan, M.J., Carlson, S.G. and Douglas, R.C.: Genes involved in MPTP neurotoxicity. Neurosci. Abstr., 1988, In press.

Lo, M.M.S., Mamalaki, C., Kadan, M.J. and Carlson, S.G.: Infected PC12 mutants selected in 1-methyl-4-phenyl pyridine (MPP+) share common retroviral integration sites. J. Biol. Chem., 1988, Submitted.

Carlson, S.G., Kadan, M.J. and Lo, M.M.S.: Coding sequence identified in a frequently mutated locus in MPP+ resistant PC12 cells. In preparation.

Kadan, M.J. and Lo, M.M.S.: Mutations conferring resistance to the neurotoxin 1-methyl-4-phenyl pyridine (MPP+). In preparation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00112-02 MPL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Drug Receptors, Neurotransmitters and Addiction

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: M.J. Kuhar Chief MPL, ARC, NIDA

Others: E.B. DeSouza Chief NBL, ARC, NIDA

G. Battaglia Staff Fellow NBL, ARC, NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

None

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.00

PROFESSIONAL:

1.25

OTHER:

0.75

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Progress on this Project has been mainly in two areas: The neurotoxic effect of substituted amphetamines; and the distribution of opiate receptors labeled by nalbuphine in brain.

MDMA is a methylated amphetamine which is currently abused. Previous neurochemical studies have suggested that administration of this drug decreases brain serotonin levels and may therefore cause a degeneration of serotonin containing neurons in brain. This Laboratory's studies have utilized a new approach: the detection of serotonin containing nerve terminals by binding to the serotonin transport sites. Findings confirm the notion that administration of these drugs results in a degeneration of serotonin containing nerve terminals since serotonin transporters labeled with paroxetine are reduced. In an extension of this Project, it has also been shown that administration of these drugs results in a loss of neurons as determined by immunocytochemical techniques. The latter studies provide direct evidence for a swelling and degeneration of serotonin containing axons and nerve terminals following MDMA administration.

## Drug Receptors, Neurotransmitters and Addiction

Nalbuphine is a potent agonist/antagonist analgesic with a low side effect profile and low abuse potential. Experiments were designed to localize the sites of nalbuphine binding to  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors in the central nervous system using in vitro labeling light microscopic autoradiography. Data suggest that nalbuphine acts on  $\mu$  and  $\kappa$  opioid receptors and the distribution of these sites found in these studies agrees with those found in earlier publications.

## Publications

Battaglia, G., Yeh, S.Y., O'Hearn, E., Molliver, M.E., Kuhar, M.J. and DeSouza, E.B.: 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxymethamphetamine destroy serotonin terminals in rat brain: Quantification of neurodegeneration by measurement of [ $^3$ H]paroxetine-labeled serotonin uptake sites. J. Pharmacol. Exp. Ther. 242: 911-916, 1987.

O'Hearn, E., Battaglia, G., DeSouza, E., Kuhar, M.J. and Molliver, M.: MDA and MDMA cause selective ablation of serotonergic axon terminals in forebrain. J. Neurosci., 1988, In press.

DeSouza, E.B., Schmidt, W.K. and Kuhar, M.J.: Nalbuphine: An autoradiographic opioid receptor binding profile in the central nervous system of an agonist/antagonist analgesic. J. Pharmacol. Exp. Ther. 244: 391-402, 1988.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00114-01 MPL
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less, Title must fit on one line between the borders.) Receptor cDNA Expression Cloning: I. Ligand Autoradiographic Screening
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	G.R. Uhl	Chief, Gene Neuroscience Unit
		MPL, ARC, NIDA
Others:	S. Iautar	Research Lab Manager
	C. Morse	Research Technician
	M.A.N. Rattray	Visiting Fellow
		MPL, ARC, NIDA
		MPL, ARC, NIDA
		MPL, ARC, NIDA

COOPERATING UNITS (if any)
None

LAB/BRANCH Molecular Pharmacology Laboratory, Neuroscience Branch
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SECTION Gene Neuroscience Unit
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
--

TOTAL MAN-YEARS: 1.50	PROFESSIONAL: 1.00	OTHER: 0.50
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CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input checked="" type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
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Cloning cDNAs encoding receptors for drugs and for the neurotransmitters impacted by drugs is an important step in the study of the genes of drug abuse. Many of these molecules are present in low abundance, and have proven difficult to purify through conventional protein biochemical approaches. The high sensitivity of receptor autoradiography is being utilized, in conjunction with the high levels of transient expression that can be engendered in mammalian cells by eukaryotic expression vectors to establish a method for directly cloning these molecules based on their ligand binding properties.

Over the past year, substantial progress has been made toward this end. Previously, it had been shown that replicas of L-cell colonies expressing apparent high affinity ligand binding sites could be identified based on a polyester-filter replica plating technique followed by receptor autoradiographic studies. The work over the current year has allowed the modification of this approach to increase the speed with which the screening cycle can be achieved, and the ease with which cDNAs can be recovered. These advances have derived from use of the transient expression vector, pCIS8, expressed in COS cells. Over the past year libraries have been constructed in the

**Receptor cDNA Expression Cloning: I. Ligand Autoradiographic Screening**

pCDM8 vector and have been characterized as containing appropriate numbers of recombinants; high affinity  $^{125}\text{I}$ -neurotensin binding sites induced in several COS cell colonies expressing portions of the library have been identified; and two plasmids which confer the ability to bind low concentrations of  $^{125}\text{I}$ -neurotensin to cells expressing them have been isolated. Goals of this Project include: Improving and documenting the quantitative efficiency of each step, adapting the method for use with tritiated radioligands, characterization of the putative positive receptor clones, and developing correlations between this method and the *Xenopus* oocyte injection paradigm (see below). If successful, this approach should allow rapid, direct cloning of genes key to the actions of several classes of abused substances.

**Publication**

Uhl, G.R.: Bind and clone: Ligand-autoradiographic receptor expression screening. Soc. Neurosci. Abstract.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  Z01 DA00115-01 MPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Receptor cDNA Expression Cloning: II. Xenopus Oocyte Expression		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: G.R. Uhl	Chief, Gene Neuroscience Unit	MPL, ARC, NIDA
Others: T. Nishimori	Visiting Scientist	MPL, ARC, NIDA
J. DiGiorgianni	Technician	MPL, ARC, NIDA
C. Spivak	Pharmacologist	NPL, ARC, NIDA
COOPERATING UNITS (if any)		
Neuropharmacology Laboratory, ARC		
LAB/BRANCH Molecular Pharmacology Laboratory, Neuroscience Branch		
SECTION Gene Neuroscience Unit		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.50	PROFESSIONAL: 0.25	OTHER: 0.25
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
<p>             Expression cloning is an attractive approach to identifying the genes and cDNAs encoding receptors for abused substances and for the neurotransmitters implicated in drug abuse. The dramatic ability of the <i>Xenopus laevis</i> oocyte to appropriately translate, post-translationally modify, and appropriately insert several receptors into its membrane has led us to establish this system as a screening tool for these cDNAs and receptors. Progress over the last several months has included: 1) Establishment of the animal colony, dissection techniques, injection techniques, and patch clamp recording apparatus necessary to assess the expression of receptors in these oocytes; 2) Establishment of a system for monitoring neurotransmitter uptake into these oocytes; 3) Documentation of the lack of an endogenous system for dopamine uptake in these oocytes. Work over the next year should allow: 1) Improvements in the ability to monitor the detailed electrical characteristics of native eggs and those injected with appropriate mRNAs. 2) Ability to assess receptor-activated electrical currents, and neurotransmitter uptake that could be induced by the expression of mRNAs purified from appropriate sources, and synthesized from cDNA libraries in vectors containing active promoters for RNA polymerases. 3) Use of this technique in conjunction with ligand-autoradiographic screening to assess the physiological relevance of ligand-binding sites conferred through expression of cDNA libraries cloned into eukaryotic expression vectors. Physiologic activities conferred to the oocyte can thus be assessed by the translation products of specific cDNAs or mRNAs. These approaches should enhance the ability to clone these DNAs without use of protein purification and protein sequencing steps.           </p>		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00116-01 MPL
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Neuronal Expression of Genes for Neurotransmitters Related to Drug Abuse

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: G.R. Uhl	Chief, Gene Neuroscience Unit	MPL, ARC, NIDA
Others: T. Nishimori	Visiting Scientist	MPL, ARC, NIDA
M. Moskowitz	Assoc. Professor	JHU
R. Maciewicz	Assoc. Professor	Harvard Medical School
J. Ryan	Research Technician	MPL, ARC, NIDA
R. Haig	Research Technician	MPL, ARC, NIDA

COOPERATING UNITS (if any)  
Departments of Neurology, Neuroscience, Pediatrics & Neurosurgery, Massachusetts General Hospital, Harvard Medical School and Howard Hughes Medical Institute. Dept. of Neuroscience, Johns Hopkins University School of Medicine.

LAB/BRANCH  
Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION  
Gene Neuroscience Unit

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 2.00	PROFESSIONAL: 1.50	OTHER: 0.50
--------------------------	-----------------------	----------------

CHECK APPROPRIATE BOX(ES)

<input type="checkbox"/> (a) Human subjects	<input checked="" type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Changes in the expression of drug-related genes in specific neurons can help to understand the impact of abused drugs on the brain. This Laboratory's previous work has established that in situ hybridization can estimate the relative levels of expression of specific genes within individual cells. In circuits where known stimuli enhance or diminish activity, the expression of the genes encoding peptide neurotransmitters is up-and-down regulated in parallel.

During the past year, cellular levels of opioid peptide mRNAs have been monitored to assess changes in the functional activity of these neurons and studies of regulated vasopressin mRNA expression to human post mortem tissue have been extended. 1) In the rat striatum, diminished expression of preproenkephalin mRNA follows lesions removing excitatory inputs. 2) Significant changes in levels of both preproenkephalin mRNA and enkephalin peptide were found following administration of morphine. These changes could play a role in the production of opiate tolerance and withdrawal symptoms. 3) Removal of sensory inputs changes neuronal expression of

**Neuronal Expression of Genes for Neurotransmitters Related to Drug Abuse**

preproenkephalin and preprodynorphin genes in the painmodulating neurons of the nucleus caudalis of the trigeminal; subpopulations of neurons seem to turn on or turn off their expression of these peptide genes with deafferentation in a fashion that could play a role in the hyperalgesia of withdrawal. 4) Levels of vasopressin mRNA in supraoptic nucleus neurons of patients who died with substantial dehydration have been monitored. These levels are enhanced with this known stimulus to augmented vasopressin release. Thus, it may be possible to study the expression of other genes more directly related to drug abuse in post mortem tissue obtained from humans abusing drugs during life.

**Publications**

Reppert, S.M. and Uhl, G.R.: The vasopressin gene is expressed prior to regulation in the supraoptic nuclei of fetal rats. Brain Res. 456: 391-396, 1988.

Nishimori, T., Moskowitz, M.A. and Uhl, G.R.: Opiate peptide gene expression in rat nucleus caudalis neurons: Normal distribution and effects of trigeminal deafferentation. J. Comp. Neurol. 274: 142, 1988.

Uhl, G.R., Navia, B. and Douglas, J.: Differential expression of preproenkephalin and preprodynorphin mRNAs in striatal neurons: High levels of preproenkephalin expression depend on cerebral cortical afferents effects of cortical lesions. J. Neurosci., In press.

Uhl, G.R., Ryan, J. and Schwartz, J.: Morphine alters preproenkephalin gene expression. Brain Res., In press.

Linnik, M.D., Sakas, D.E., Uhl, G.R. and Moskowitz, M.A.: V nerve neuropeptides and post-SAH headaches: Subarachnoid blood alters tachykinin gene expression in the trigeminovascular system. Ann. Neurol., In press.

Schwartz, J.P., Simantov, R., Ryan, J.P. and Uhl, G.R.: Control of striatal enkephalin gene expression. Proceed. VII Int. Congress of Endocrinology, In press.

Stopa, E.G., Uhl, G.R., Mobtaker, H., Winnepenny, R., Hoefler, H., King, J.C., Bird, E.D. and Wolfe, H.: Somatostatin-gene expression in human brains: In situ hybridization studies in post mortem tissue. Arch. Path., Submitted.

## Publications (Cont'd)

Rivkees, S.A., Chaar, M.R., Hanley, D.F., Maxwell, M., Reppert, S.M. and Uhl, G.R.: Localization and regulation of vasopressin mRNA in human neurons. Synapse, Submitted.

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## 2. Neuropharmacology Laboratory — Edythe D. London, Ph.D., Chief

### Overview

The Neuropharmacology Laboratory conducts studies designed to elucidate neurochemical and electrophysiological mechanisms, and brain loci that mediate the behavioral and physiological effects of abused drugs. As part of this effort, studies are conducted to determine acute and chronic effects of abused drugs in biochemical and electrophysiological systems as well as in intact organisms. Major areas of concentration include studies on responses to opioids, psychomotor stimulants, and nicotine. Efforts are directed to elucidate basic neurochemical mechanisms involving neurotransmitter systems that may impact upon the actions of abused drugs. Elucidation of endocrine, nutritional or other factors which might modify transmission in pathways important to the effects of abused drugs is also a major objective. Acquisition of such information could be helpful in the design of treatment strategies for substance abuse.

The Laboratory functions as three cooperating units: the Cerebral Metabolism Unit (Dr. E.D. London, Chief); the Neurochemistry Unit (Dr. T.-P. Su, Chief); and the Neurophysiology Unit (Drs. J. Bell and C. Spivak, Chiefs). A wide variety of approaches is used to relate neurochemical findings to physiological measures in vitro and physiological and behavioral measures in whole animals and human volunteers. Techniques utilized include receptor binding assays, purification and identification of endogenous neuroactive substances, electrophysiological studies of single neurons and neuronal circuits, isolated tissue bath preparations, and cerebral metabolic mapping in human volunteers and laboratory animals, using positron emission tomography (PET) and quantitative autoradiography, respectively.

Collaborative studies involve the Psychopathology and Cognitive Studies Branch, ARC; the Preclinical Pharmacology Branch, ARC; the Division of Nuclear Medicine, The Johns Hopkins Medical Institutions (JHMI); and the Department of Pharmacology and Toxicology, University of Maryland School of Pharmacy.

### Summary of Ongoing Research

#### A. Cerebral Metabolic Studies to Delineate Anatomical Substrates of the Effects of Abused Drugs

The objective of these studies is to identify those brain areas that are activated or inhibited by acute and chronic administration of abused drugs. It is hoped that the information obtained will lead to a better understanding of the mechanisms involved in drug self-

administration, tolerance and dependence. The approach that has been used involves mapping and quantitation of regional cerebral metabolic rates for glucose (rCMRglu) in human volunteers and rats, using PET and ex vivo quantitative autoradiography, respectively.

Using the PET [<sup>18</sup>F]fluorodeoxyglucose (FDG) method in human volunteers and a double-blind crossover design, it was shown that a dose of morphine which was rated as euphorigenic in subjective self-reports reduced rCMRglu in some telencephalic areas to a statistically significant extent, with no statistically significant effect in lower brain areas.

Similar findings have been obtained in a protocol in which cocaine was administered intravenously. The results of the two studies, taken together with previous reports that other abused drugs (barbiturates, benzodiazepines, and amphetamine) also reduce telencephalic glucose utilization, suggest that the reduction of telencephalic function, as indicated by rCMRglu, contributes to, or is a consequence of, drug-induced reward/reinforcement.

Studies in rats have made it possible to achieve greater anatomical resolution than that obtained with PET, but have been limited by the inability to relate cerebral metabolic findings directly to simultaneous effects on mood and feeling state. Responses to abused drugs from several drug classes have been studied. Particular attention has been given to opioids and psychomotor stimulants. The  $\mu$  agonists, morphine and oxymorphone, were found to decrease glucose utilization in thalamic nuclei, including some of those areas which have been implicated in somatosensory processing. Nalbuphine, which has kappa agonist and  $\mu$  antagonist properties, did not produce these effects, but stimulated LCGU in the spinal tract of the trigeminal nerve. These findings suggest that different supraspinal mechanisms mediate the actions of  $\mu$  versus kappa opioids. Cocaine and 3,4-methylene-dioxymethamphetamine (MDMA) stimulated rCMRglu in components of the extrapyramidal motor system and reduced rCMRglu in the lateral habenula. Moreover, a greater sensitivity to cocaine was observed in the responses of Lewis rats as compared with the Fischer rats, suggestive of a genetic difference. MDMA also produced activation in some thalamic nuclei and the visual cortex. The findings were consistent with a psychomotor stimulant action of MDMA, similar to that of cocaine and amphetamine, and with the production of visual hallucinations by MDMA in humans.

Projected work in this area will assess effects of cocaine on regional cerebral blood flow (rCBF) in humans using techniques that potentially allow greater time resolution and anatomical localization than that obtained with FDG. The objective is to relate effects of cocaine on specific feeling states (e.g., rush, feeling good, craving) to changes in rCBF. In addition, the effects

of morphine and cocaine on electroencephalographic (EEG) parameters will be related to subjective effects as well as to PET findings.

**B. Studies of Physiological and Metabolic Effects of Acute and Chronic Opioid Treatments and the Opioid Abstinence Syndrome**

This project is designed to help elucidate the physiological effects of morphine. Other objectives include the delineation of anatomical systems in rat brain and spinal cord that may mediate the acute and chronic effects of opioid agonists and antagonists, and that may contribute to the opioid abstinence syndrome.

Several lines of evidence indicate that the physiological effects of opioids on cellular membranes involve the calcium ion. Thus, an understanding of the role of calcium in opioid effects may be fundamental to elucidating mechanisms underlying the acute effects of opioids, as well as tolerance and physical dependence. An extension of earlier work in this Laboratory, which demonstrated antagonism of opioid-induced respiratory depression and tachycardia by calcium channel antagonists, revealed that the antagonism was not due to altered morphine pharmacokinetics which would logically affect all of morphine's effects in a similar direction. Thus, this approach or an analogous one could conceivably result in antagonism of the respiratory depressant effects of opioids with simultaneous facilitation of analgesia, leading to drug combinations with fewer opioid side effects and less potential for tolerance and physical dependence. With this as background, the projected studies would focus on interactions between opioids and calcium channel antagonists in human volunteers; euphoria and other acute effects associated with opioids would be the study parameters.

Studies of the opioid abstinence syndrome have provided valuable insight into mechanisms of opioid tolerance and withdrawal, and are relevant to the clinical management of opioid abuse. In vivo studies in rats demonstrated complete tolerance to subchronic morphine treatment on cerebral metabolism, but marked hypermetabolism was found to be induced during naloxone-precipitated morphine withdrawal. Cerebral and spinal hypermetabolism during morphine withdrawal, as well as their antagonism by clonidine, showed a wide distribution in the rat brain, with involvement of various limbic and hypothalamic areas not previously implicated in these phenomena. Further, studies on the isolated spinal cord of the neonatal rat have provided electrophysiological evidence that suggests that increased release of substance P from primary afferents may contribute to the opioid withdrawal syndrome. Moreover, evidence from electrophysiological and autoradiographic studies has suggested that corticotropin-releasing factor (CRF) is a primary afferent neurotransmitter in the neonatal rat spinal cord.



Previous studies in this Laboratory have shown that presynaptic changes contribute to opioid withdrawal in the isolated spinal cord of the neonatal rat. However, the role of postsynaptic changes in spinal withdrawal is unknown. In view of the complexity of intact systems such as the isolated spinal cord, a major effort in the Laboratory has involved implementing equipment and developing tissue culture techniques for studying primary cultures of rat spinal cord. Moreover, plans have been developed to utilize electrophysiological techniques in an effort to determine if postsynaptic changes in dorsal horn neurons contribute to the opioid abstinence syndrome.

Since substance P has been proposed as a transmitter in nociceptive primary afferent neurons, studies were performed with capsaicin, a peptide which depletes substance P. After subchronic capsaicin treatment, a challenge dose of capsaicin was found to stimulate glucose utilization in dorsal column and brain stem nuclei which receive primary sensory afferent input, or are important in autonomic functions. Following subchronic treatment with a greater cumulative dose of capsaicin, a challenge dose was not found to stimulate glucose utilization in the hindbrain. The findings provide evidence for a central component of the stimulation and subsequent insensitivity observed with continued capsaicin treatment.

#### **C. Biochemical and Behavioral Studies of Kappa Opioid Interactions**

Since the discovery of the multiplicity of opioid receptor subtypes, the elucidation of the physiological roles of the various subtypes of receptors has been a research area of intense interest. Current studies focus on delineating the importance of kappa opioid receptors in various systems. It was determined that kappa receptors are remarkably stable to postmortem decay, a prerequisite for studies of these receptors in postmortem human tissue. Additionally, an evaluation of the interactions of volatile anesthetics and mu and kappa opioid receptor binding sites demonstrated differential effects on these two receptor subpopulations. The results indicated that, although volatile anesthetics may have some membrane effects in common with opioid-receptor interactions, the different agents have certain unique interactions that vary with the anesthetic compound and receptor population studied.

Studies directed at understanding the role of opioid mechanisms in various physiological functions have implicated an opioid involvement in hibernation. The findings suggest that kappa receptors, which may not be involved in the induction of hibernation, may be involved in the arousal stage of hibernation. In contrast, delta receptors appear to have a role in the induction of hibernation

summer-active ground squirrels. Possible involvement of other opioid receptor subtypes is being evaluated.

The well-recognized diuretic effect of kappa agonists in rats, coupled with the observation that the synthetic pentapeptide, BW942C, a mu opioid agonist, produced diuresis in humans, have suggested that BW942C possesses kappa agonist activity. BW942C apparently may be the first peptide characterized as a partial kappa agonist.

#### D. The Biological Role of the Sigma System

A major effort has been directed toward the elucidation discovery of the biological role of sigma binding sites, which may represent a link between the brain, the endocrine system, and the immune system. These sites, which were initially characterized in rodent and human brain and lymphoid tissue, have affinities for steroid hormone receptors which correspond to the activity of hormones in an anti-inflammatory assay. Efforts to purify and identify an endogenous ligand for the sigma binding site and to develop a bioassay system for sigma ligands have continued. Additionally, several research projects have sought to identify functional effects which may be attributed to interactions at sigma sites. A cultured cell line (NCB 20) that expresses sigma receptors is being utilized for electrophysiological studies and electrical effects altered by sigma agonists and antagonists have been characterized by voltage clamp and patch clamp techniques. Preliminary evidence has identified the potassium leak conductance ion channel as a target of sigma action.

Despite many commonalities between the biochemical and behavioral effects of ligands for sigma receptors and phencyclidine (PCP) analogues, studies during the past year have demonstrated distinctions between the actions of these groups of drugs. While the prototypic ligands for PCP and sigma receptors, d-N-allylnormetazocine (d-NANM) and PCP, respectively, cross-react in binding assays, and produce some of the same behavioral effects, these drugs produce different patterns of effects on local cerebral metabolism. Furthermore, field-stimulated contractions of the isolated guinea-pig vas deferens from young adult guinea-pigs have been found to be potentiated by d-NANM, but not by PCP. Moreover, receptor binding studies have revealed differences in the phylogenetic and developmental courses for the two binding sites in neural tissue. In addition, in vivo binding of ligands for both PCP receptors and sigma binding sites has been demonstrated in the mouse brain.

Future directions for this area of research include the following: (1) final purification and characterization of sigmaparin; (2) studies of the subcellular localization and biochemical



interactions of sigma binding sites in guinea pig brain; (3) pharmacological characterization of sigma binding sites in the guinea pig vas deferens; (4) further elucidation, using electrophysiological techniques, of the functional consequences of sigma receptor interactions; and, (5) imaging of sigma and PCP receptors using PET.

#### **E. Interactions at Cerebral and Peripheral Nicotinic Receptors - Relation to the Behavioral and Physiological Effects of Nicotine**

This project is directed toward elucidating the actions of nicotine at various levels of organization, from the ion channel to the whole animal. The importance of this project stems from the following: (1) nicotine is a prototypic drug of abuse; (2) receptor and ion channel interactions which mediate the action of nicotine are fundamental to processes involving acetylcholine, a major neurotransmitter in the brain and periphery; and (3) interactions at nicotinic synapses and related ion channels represent a model for coupling receptor-mediated events to biological processes.

A study on the drug-receptor interaction at the neuromuscular nicotinic acetylcholine receptor is being concluded this year. New semi-rigid agonists were synthesized, modeled by molecular mechanics and molecular orbital calculations, and tested for their distortion of the receptor's ion channel using patch clamp recording. Subtle changes in agonist structure and electrostatic profile were correlated with activity.

Ongoing studies focus on the cerebral distribution of responses to nicotine, a prototypic drug of abuse. Acute treatment with nicotine was found to stimulate cerebral glucose utilization in a pattern that closely followed the distribution of receptors for radiolabelled nicotine in vitro. Moreover, studies of chronic nicotine effects on LCGU and in vivo mapping of the nicotinic receptor with radiolabelled nicotine have provided important clues about the neuroanatomical substrates involved in the action of this compound. These studies will lay the groundwork for the development of <sup>11</sup>C-N-methylnicotine as a probe for studying nicotinic receptors in the human brain with PET.

#### **F. Immune Effects of Chronic Drug Abuse**

Since drug abusers are at high risk for infection by human immunodeficiency virus (HIV), several studies related to immunopharmacology and treatment of central nervous system (CNS) infection by HIV have been continued. It was of interest to determine if abused drugs, especially those commonly abused by intravenous injection, affect immune function. Ongoing studies demonstrated a dose-dependent reduction of circulating T-lymphocytes associated with chronic morphine treatment in the mouse,



indicating that immunocompetency may be compromised by use of this drug. The extension of this study will focus on the specificity of the immunological effect, attempting to identify specific neurohumoral factors or receptors which might mediate the immunosuppressive effects of opioids and other abused drugs. Other studies would focus on identifying the sites and mechanism of action of peptide T and GP-120, a potential therapeutic agent and a component of the HIV viral protein coat, respectively.

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## Abstracts (Cont'd)

Waller, S.B., Ball, J. and London, E.D.: The neocortical and hippocampal cholinergic nervous systems in dementia: A neurochemical examination. Annual Meeting of the American Gerontological Society. San Francisco, November 18-22, 1988. Gerontologist, In press.

London, E.D., Jaffe, J.H., Cascella, N.G., Sano, M., Herning, R.I., Links, J., Wong, D.F., Dannals, R.F., Grayson, R. and Wagner, H.N., Jr.: Acute cocaine decreases regional cerebral glucose utilization in human substance abusers. Annual Meeting of American College of Neuropsychopharmacology. San Juan, Puerto Rico, December 11-16, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER ZO1 DA00003-04 NPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Investigations of Kappa and Sigma Properties of Antinociceptive Drugs in the Dog		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) PI: D.B. Vaupel                      Pharmacologist                      NPL, ARC, NIDA  Others: E.J. Cone                      Chief                      CDM, ARC, NIDA B. Nickel                      Research Associate                      Degussa Pharma		
COOPERATING UNITS (if any) Degussa Pharma, Frankfurt, Federal Republic of Germany Laboratory of Chemistry & Drug Metabolism, Clinical Biology Branch, ARC		
LAB/BRANCH Neuropharmacology Laboratory/Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.10	PROFESSIONAL: 0.10	OTHER: 0.00
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>It was previously demonstrated that the pharmacologic activity of d,1-ketocyclazocine is associated with the l-enantiomer, with the d-form being inactive. To show that the actions of l-ketocyclazocine represent kappa and not mu effects, selective antagonism studies with naltrexone were conducted. Low doses of naltrexone (0.01 mg/kg) antagonized morphine, whereas high doses (1 mg/kg) were needed to antagonize d,1-ketocyclazocine, thus demonstrating that the agonist actions of d,1-ketocyclazocine can be classified as being of the kappa type in the chronic spinal dog.</p> <p>Flupirtine is a new analgesic whose mechanism of action is unknown. To assess the role of opioid mechanisms in flupirtine-induced antinociception, flupirtine was compared to the opioid agonist pentazocine using both single dose and naltrexone antagonism studies in the chronic spinal dog. It was concluded that flupirtine-induced antinociception is not opiate receptor mediated and occurs primarily at supraspinal sites. Its antinociceptive potency was estimated to be 1/12th that of pentazocine in the dog.</p>		

**Investigations of Kappa and Sigma Properties of Antinociceptive Drugs in the Dog**

The acute interactions of pentazocine and tripeleennamine, in ratios that have been abused by humans, have been evaluated in the chronic spinal dog. No consistent pattern among the interactions emerged. Depending on the parameter, the interactions showed that the effects of tripeleennamine summated algebraically with the effects of pentazocine or antagonized them. Naltrexone antagonized pentazocine, but not tripeleennamine; and tripeleennamine failed to antagonize the sigma-like activity of SKF-10047. While such interactions may contribute to the abuse liability of tripeleennamine and pentazocine, the tripeleennamine component does not appear to be opioid-like. Furthermore, tripeleennamine does not antagonize sigma activity, which has been suggested as a mechanism for canine dysphoria.

The future course of this project is to prepare this work for publication.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER ZO1 DA00200-03 NPL
PERIOD COVERED <b>October 1, 1987 to December 31, 1988</b>		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Cerebral Metabolic Studies of Drug Effects on Mood and Performance</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)  PI:        E.D. London                      Chief                                      NPL, ARC, NIDA  Others: *		
COOPERATING UNITS (if any)  BPVL, CHP, RSB of ARC, Vanderbilt University; Johns Hopkins Medical Institutions (JHMI), Aberdeen Proving Ground, MD.		
LAB/BRANCH		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 2.40	PROFESSIONAL: 2.10	OTHER: 0.30
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>           This project uses metabolic mapping and positron emission tomography (PET) to attain the following objectives: (1) to identify brain areas related to drug effects on mood; (2) to assess relations between brain metabolic and electrical activities; and (3) to correlate personality traits or performance deficits with brain metabolic activity. Ongoing projects focus on the effects of morphine and cocaine.         </p> <p>           Human volunteers between 21 and 45 years of age with histories of polydrug abuse, but no drug dependencies except nicotine, participated in two double-blind, placebo-controlled crossover studies. The studies compared effects of morphine and cocaine with those of placebo on the regional cerebral metabolic rate for glucose (rCMRglu), measured by the PET [<sup>18</sup>F]fluorodeoxyglucose (FDG) method. Rates of rCMRglu were measured in 50 areas from both hemispheres. In simulation tests before PET, spontaneous EEG was recorded in addition to self-reports on the strength and quality of drug effects and the subject's liking for them. The effects of morphine were studied in 12 subjects. A 30 mg (i.m.) dose of morphine, which was judged to be euphorigenic by the subjects, produced EEG slowing to a statistically significant degree and decreased rCMRglu in whole brain and in 12 of 19 cortical areas, the hippocampus and the basal ganglia.         </p>		

### Cerebral Metabolic Studies of Drug Effects on Mood and Performance

No statistically significant differences were observed between morphine and placebo were seen in subcortical areas, nor were there morphine-induced increases in rCMRglu documented. In 5 subjects, 40 mg cocaine increased EEG beta activity and produced euphoria, as measured by visual analogue scales and standard questionnaires. Cocaine reduced global cerebral glucose utilization and rCMRglu in telencephalic areas. Despite this, some areas exhibited no statistically significant changes, and no cocaine-induced increases in rCMRglu were observed.

The finding that both morphine and cocaine, in euphorigenic doses, reduced telencephalic rCMRglu, despite differences in their pharmacology and spectrum of behavioral effects, suggests that a reduction of telencephalic rCMRglu may be involved in the mechanism by which abused drugs produce positive feelings in humans.

### Publications

London, E.D: Effects of abused drugs on cerebral glucose metabolism. J. Neuropsychiat. Clin. Neurosci., In press.

### \* Other investigators on this project include:

E.P. Broussole	Visiting Fellow	NPL, ARC, NIDA
R.I. Herning	Visiting Scientist	CHP, ARC, NIDA
L.R. Rippetoe	Head Nurse	ARC, NIDA
N.G. Cascella	Visiting Fellow	NPL, ARC, NIDA
M. Sano	Visiting Scientist	NPL, ARC, NIDA
R.W. Margolin		Vanderbilt U.
J.M. Links		JHMI
H.N. Wagner, Jr.		JHMI
J.K.T. Young		JHMI
D.F. Wong		JHMI

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER ZO1 DA00201-04 NPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Toxic and Metabolic Effects of Cocaine and 3,4-Methylenedioxymethamphetamine		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: E.D. London Others: A.S. Kimes G. Wilkerson J. Johnson A.D. Weissman S.R. Cohen A. Della Puppa	Chief Visiting Scientist Laboratory Technician Visiting Scientist Staff Fellow Visiting Fellow Visiting Fellow	NPL, ARC, NIDA NPL, ARC, NIDA NPL, ARC, NIDA NPL, ARC, NIDA NPL, ARC, NIDA NPL, ARC, NIDA NPL, ARC, NIDA
COOPERATING UNITS (if any)  Molecular Pharmacology Laboratory, Neuroscience Branch,		
LAB/BRANCH Neuropharmacology Laboratory/Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 1.05	PROFESSIONAL: 0.55	OTHER: 0.50
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Effects of cocaine and methylenedioxymethamphetamine, (MDMA, "Ecstasy") were studied and compared. An objective was to identify common actions of the drugs. Such commonalities might relate to the psychomotor stimulant and reinforcing properties of the drugs.</p> <p>Cocaine was found to stimulate the regional metabolic rate for glucose (rCMRglu) in components of the extrapyramidal motor system, but to reduce rCMRglu in the lateral habenula of Fischer-344 and Lewis rats. It appeared that Lewis rats were more sensitive to the cerebral metabolic and behavioral effects (stereotypy) of cocaine, consistent with the view that genetic differences in sensitivity to cocaine influence the susceptibility to cocaine's abuse potential.</p> <p>Ultrastructural effects of cocaine on neural tissue were studied using NG108X15 neuroblastoma cells. Cells were treated with cocaine for 1-3 days. Cocaine decreased cell viability and caused the appearance of dense bodies and nuclear abnormalities (invaginations, disruption of the nuclear membrane). The results suggested that cocaine may interfere with cell replication and may be neurotoxic.</p>		



**Toxic and Metabolic Effects of Cocaine and 3,4-Methylene-dioxymethamphetamine**

MDMA produced marked stereotypies and stimulated rCMRglu in areas associated with extrapyramidal motor, visual and limbic functions. Except for the effects in the visual system, the findings resembled those obtained with cocaine.

Increased metabolism in extrapyramidal brain regions in response to psychomotor stimulants (i.e., cocaine, MDMA, amphetamine and phencyclidine) was also apparent during muscle paralysis and artificial ventilation, indicating the rCMRglu responses in these areas were not secondary to increased movement.

**Publications**

Johnson, J.E., Jr. and Weissman, A.D.: Cocaine's chronic effects on the fine structure of a neuroglioblastoma cell line NG108x15. Brain Res. Bull. 20: 39-47.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  ZO1 DA00202-05 NPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Physiological and Metabolic Effects of Opioids and the Opioid Abstinence Syndrome		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.D. London	Chief NPL, ARC, NIDA
Others:	R.J. Fanelli	Staff Fellow NPL, ARC, NIDA
	A.S. Kimes	Visiting Scientist NPL, ARC, NIDA
	J.A. Bell	Pharmacologist NPL, ARC, NIDA
	E.B. DeSouza	Visiting Associate NPL, ARC, NIDA
	M. Szikszay	Visiting Fellow NPL, ARC, NIDA
	A. Della Puppa	Visiting Fellow NPL, ARC, NIDA
COOPERATING UNITS (if any)  Molecular Pharmacology Laboratory (MPL), Neuroscience Branch, ARC		
LAB/BRANCH Neuropharmacology Laboratory/Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.35	1.05	0.30
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither		
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unraduced type. Do not exceed the space provided.)		
<p>This project is aimed at delineating the physiological effects of opioids and the central nervous system sites that mediate opioid agonists and antagonists, which are related to somatosensory processing and the opioid abstinence syndrome.</p> <p>The time course of the interaction of verapamil with morphine on physiological parameters as well as with the pharmacokinetics of morphine have been studied in Fischer-344 rats. The interactions observed with these two compounds on respiration, blood pH, blood pressure and heart rate were complex and not related to the influence of verapamil on morphine pharmacokinetics.</p> <p>The deoxyglucose method was used to measure the regional metabolic rate for glucose (rCMRglu) in the rat. Mu agonists decreased rCMRglu in limbic regions and several somatosensory processing areas. Nalbuphine, a kappa agonist/mu antagonist, stimulated rCMRglu in trigeminal nerve nuclei, suggesting that different supraspinal mechanisms mediate the actions of kappa versus mu opioids. Capsaicin, which releases substance P, stimulated rCMRglu in dorsal column and other brainstem nuclei, indicating that metabolic mapping might be useful in delineating the neuroanatomical areas mediating the sensory and autonomic effects of capsaicin.</p>		

**Physiological and Metabolic Effects of Opioids and the Opioid Abstinence Syndrome**

Electrophysiological studies provided evidence that corticotropin-releasing factor activates neurons in superficial dorsal horn presynaptic to motoneurons, directly depolarizes motoneurons, and could play a role in opioid abstinence. Projected studies include investigations of calcium antagonist interactions with opioid effects in humans and electrophysiological studies of the mechanisms of the opioid abstinence syndrome at the neuronal level.

**Publications**

Fanelli, R.J., Szikszay, M., Jasinski, D.R. and London, E.D.: Differential effects of mu and kappa opioid analgesics on local cerebral glucose utilization. Brain Res. 422: 257-266, 1987.

London, E.D., Kimes, A.S. and Fanelli, R.J.: Cerebral metabolic effects of morphine in the rat. Substance Abuse 8: 43-52, 1987.

Bell, J.A. and Shannon, H.E.: Mu opioid partial agonists: Facilitative effects on electrophysiologically recorded C-fiber reflexes in the cat. Neuropharmacology 27: 649-652, 1988.

Bell, J.A., Kimes, A.S. and London, E.D.: Increased glucose utilization in superficial layers of the rat spinal dorsal horn during precipitated morphine withdrawal. Eur. J. Pharmacol. 150: 171-174, 1988.

Szikszay, M. and London, E.D.: Effects of subacute capsaicin treatment on local cerebral glucose utilization in the rat. Neurosci. 25: 917-923, 1987.

Fanelli, R.J., Walovitch, R.C., Jasinski, D.R. and London, E.D.: Naloxone fails to alter local cerebral glucose utilization in the rat. Pharmacol. Biochem. Behav., In press.

Bell, J.A. and DeSouza, E.B.: Functional corticotropin-releasing factor receptors in neonatal rat spinal cord. Peptides, In press.

Kimes, A.S. and London, E.D.: Glucose utilization in the rat brain during chronic morphine treatment and naloxone-precipitated morphine withdrawal. J. Pharmacol. Exp. Ther., In press.





## Biological Roles and Mechanisms Involving Sigma and Phencyclidine Receptor Binding

Cerebral metabolic studies in rats demonstrated different responses to sigma ligands as compared with PCP, supporting the view that the sigma and PCP receptors may be functionally differentiated. Self-administration of PCP by rats produced effects on rCMRglu in the nucleus accumbens and cingulate cortex which were not seen after acute PCP treatment in naive rats which were not trained to self-administer PCP.

Projected studies include in vivo labelling of sigma and PCP receptors for PET imaging, verification and elucidation of the function of cerebral microsome sigma receptors, definition of the function of sigma receptors at ion channels, and elucidation of factors which may influence PCP receptor interactions.

## Publications

Weissman, A.D., Dam, M. and London, E.D.: Selective alterations in cerebral glucose utilization induced by phencyclidine. Brain Res. 435: 29-40, 1987.

London, E.D., Dam, M. and Weissman, A.D.: Different Patterns of Cerebral Glucose Utilization Produced by Phencyclidine and D-N-Allylnormetazocine. In Domino, E.F. and Kamenka, J.M. (Eds): Proceedings of the Second U.S.-French Sponsored International Seminar: Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology. Ann Arbor, MI, NPP Books, 1988, pp. 197-307.

Vaupel, D.B. and Su, T.-P.: A Potential Bioassay for Identifying PCP and Sigma Ligands Using the Guinea Pig Vas Deferens (GPVD). In Domino, E.F. and Kamenka, J.M. (Eds.): Proceedings of the Second U.S.-French Sponsored International Seminar: Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology. Ann Arbor, MI, NPP Books, 1988, pp. 473-482.

Su, T.-P., London, E.D. and Jaffe, J.H.: Steroid binding at sigma receptors suggests a link between endocrine, nervous and immune systems. Science 240: 219-221, 1988.

Su, T.-P., Schell, S.E., Ford-Rice, F.Y. and London, E.D.: Correlation of inhibitory potencies of putative antagonists for sigma receptors in brain and spleen. Eur. J. Pharmacol. 148: 467-470.

Weissman, A.D., Su, T.-P., Hedreen, J.C. and London, E.D.: Sigma receptors in post-mortem human brains. J. Pharmacol. Exp. Ther., In press.

**Biological Roles and Mechanisms Involving Sigma and Phencyclidine Receptor Binding**

\* Other investigators involved in this Project are:

E.P. Broussole	Visiting Fellow	NPL, ARC, NIDA
K. Marquis	Postdoctoral Fellow	U of MD
T.H. Vu	Guest Worker	NPL, ARC, NIDA
M.D. Majewska	Senior Staff Fellow	NPL, ARC, NIDA
C.E. Spivak	Pharmacologist	NPL, ARC, NIDA
J. Hedreen	Asst. Professor	JHMI
D.B. Vaupel	Pharmacologist	NPL, ARC, NIDA
J.E. Moreton	Professor	U of MD
J.A. Bell	Pharmacologist	NPL, ARC, NIDA
X. Wu	Visiting Fellow	NPL, ARC, NIDA
A.D. Weissman	Staff Fellow	NPL, ARC, NIDA
A. Della Puppa	Visiting Fellow	NPL, ARC, NIDA



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 DA00207-04 NPL
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Nicotinic Receptors and the Behavioral and Metabolic Effects of Nicotine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.D. London	Chief	NPL, ARC, NIDA
Others:	R. J. Fanelli	Staff Fellow	NPL, ARC, NIDA
	E.P. Broussole	Visiting Scientist	NPL, ARC, NIDA
	A.S. Kimes	Visiting Scientist	NPL, ARC, NIDA
	M.D. Majewska	Senior Staff Fellow	NPL, ARC, NIDA
	H. Takayama	Guest Worker	NPL, ARC, NIDA

COOPERATING UNITS (if any)

Biology of Dependence and Abuse Potential Assessment (BDL), Clinical Biology Branch

LAB/BRANCH  
Neuropharmacology Laboratory/Neuroscience Branch

SECTION

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 1.15	PROFESSIONAL: 0.90	OTHER: 0.25
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CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
☐ (b) Human tissues
☒ (c) Neither
- ☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Previous studies demonstrated saturable, specific binding of [<sup>3</sup>H]-nicotine in the rat brain using light microscopic autoradiography. Aims of this project are to elucidate receptor mechanisms involved in the behavioral effects of nicotine and to provide additional information about nicotine receptors so that this might ultimately be studied in the human brain with positron emission tomography.

[<sup>3</sup>H]1-nicotine was injected intravenously in mice which were sacrificed at various times thereafter. Brains were dissected for measurement of radioactivity. Nonspecific binding was determined in mice pretreated with unlabelled 1-nicotine. There was a rapid entry of [<sup>3</sup>H]nicotine into the brain (maximum at 5 minutes) and specific binding was heterogeneously distributed. For example, levels were highest in medial and posterior cortex and thalamus/hypothalamus; intermediate in frontal cortex, cerebellum and caudate-putamen; and lowest in hippocampus and olfactory bulb. Nicotinic agonists significantly inhibited binding, while several nicotinic antagonists were inactive. These results suggest that specific binding of [<sup>3</sup>H] nicotine can be measured in vivo with radiolabelled nicotine.

## Nicotinic Receptors and the Behavioral and Metabolic Effects of Nicotine

Studies were performed in rats to determine the effects of acute and chronic treatment with nicotine on regional cerebral metabolic rates for glucose (rCMRglu), measured by the 2-deoxy-D-[1-<sup>14</sup>C]glucose method. Acute nicotine stimulated rCMRglu in drug-naive rats in a pattern closely paralleling the distribution of specific binding sites for [<sup>3</sup>H]nicotine, suggesting that the sites are true receptors coupled to cerebral metabolism. Chronic nicotine treatment produced sensitization which was observed with some behavioral responses, but not with rCMRglu. Chronic nicotine reduced basal rCMRglu in the superior colliculus and produced tolerance seen as a reduced response to nicotine challenge in the lateral geniculate body. Future studies will focus primarily on nicotine effects in humans and on nicotine withdrawal.

## Publications

London, E.D., Dam, M. and Fanelli, R.J.: Nicotine enhances cerebral glucose utilization in central components of the rat visual system. Brain Res. Bull. 20: 381-385, 1988.

London, E.D., Connolly, R.J., Szikszay, M., Wamsley, J.K. and Dam, M.: Effects of nicotine on local cerebral glucose utilization in the rat. J. Neurosci., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  ZO1 DA00208-04 NPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Studies on Localization and Mechanisms of Action of Anxiolytics</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: E.D. London	Chief	NPL, ARC, NIDA
Others: M. Dam	Visiting Scientist	NPL, ARC, NIDA
E.P. Broussole	Visiting Fellow	NPL, ARC, NIDA
M.D. Majewska	Senior Staff Fellow	NPL, ARC, NIDA
COOPERATING UNITS (if any)  None		
LAB/BRANCH Neuropharmacology Laboratory/Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.25	PROFESSIONAL: 0.25	OTHER: 0.00
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  The 2-deoxy-D[1- <sup>14</sup> C]-glucose (2-DG) method was used to assess the acute effects of diazepam and CL 218,872 on the regional metabolic rate for glucose (rCMRglu) in awake rats. Diazepam, 2.5 mg/kg, i.v., 2 minutes before 2-DG, decreased rCMRglu in 15 of 61 brain regions examined, but increased rCMRglu in the superior colliculus. A higher dose (5 mg/kg) produced greater decrements and affected more areas. Most rCMRglu effects of 5 mg/kg diazepam occurred at 2 minutes and were also seen in rats treated 30 minutes, but not 180 minutes, before 2-DG. The rCMRglu decrements occurred preferentially in areas rich in type I benzodiazepine receptors (i.e., cerebellum, globus pallidus, thalamus, and cerebral cortex), compared to those with high densities of type II receptors (i.e., caudate-putamen, nucleus accumbens, and dentate gyrus). CL 218,872 (5 mg/kg; i.p.; 30 minutes before 2-DG) did not affect rCMRglu, but 10 mg/kg reduced rCMRglu in a pattern which resembled the effects of diazepam. Exceptions were seen in the globus pallidus, where diazepam, but not CL 218,872, reduced rCMRglu and in the dentate gyrus, in which CL 218,872, but not diazepam, reduced rCMRglu at all of the dosages used. These findings provide information about neuroanatomical sites that may be important to the behavioral effects of diazepam and CL 218,872, and are consistent with a functional distinction between type I and type II benzodiazepine receptors.		



**Studies on Localization and Mechanisms of Action of Anxiolytics**

The gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex was also studied. The sensitivity of GABA-A receptors in the brains of rats was increased during pregnancy, and was reduced dramatically in puerperium. These effects, which are apparently due to an action of GABA agonistic steroids, may explain some of the psychological changes accompanying human pregnancy (if they also occur in humans), such as the feeling of well-being during pregnancy, and postpartum depression.

The future course for this project is to prepare this work for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER ZO1 DA00209-05 NPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Factors Which Influence Regional Cerebral Metabolic Rates for Glucose</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: E.D. London	Chief	NPL, ARC, NIDA
Others: I.R. Cohen	Research Fellow	University of MD
N.G. Weiland	Research Fellow	University of MD
P.M. Wise	Associate Professor	University of MD
A. Della Puppa	Visiting Fellow	NPL, ARC, NIDA
COOPERATING UNITS (if any)  Department of Physiology, University of Maryland		
LAB/BRANCH Neuropharmacology Laboratory/Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.35	PROFESSIONAL: 0.25	OTHER: 0.10
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>The regional cerebral metabolic rate for glucose (rCMRglu) is used extensively as an index of brain function. Therefore, it is important to consider the potential influences of various physiological and psychological factors in interpreting the effects of psychoactive drugs on rCMRglu. Thus, studies were initiated on the effects of various conditions on rCMRglu, measured by the 2-deoxy-D-[1-<sup>14</sup>C]glucose method in the rat. Factors considered include age, endocrine status, circadian periodicity, pain, and neurodegenerative changes.</p> <p>Studies in young and old ovariectomized rats demonstrated a diurnal rhythmicity in rCMRglu of the suprachiasmatic nucleus and pineal gland. Although there was no age difference in glucose utilization of the pineal gland, rCMRglu was reduced during the light and dark in all hypothalamic areas examined except the suprachiasmatic preoptic nucleus and the median eminence. Middle-aged rats primed with estradiol showed irregularity in the circadian periodicity of rCMRglu in the suprachiasmatic nucleus, associated with a loss of cyclic reproductive function.</p>		

## Factors Which Influence Regional Cerebral Metabolic Rates for Glucose

A study to explore the effects of neurodegeneration associated with the "ECC-syndrome" (excitatory, circling, choreoathetoid neck movements) produced by the neurotoxin, iminodipropionitrile (IDPN), suggested that effects of IDPN on nigrotectal pathways could play a role in the IDPN-induced persistent spasmodic dyskinetic syndrome. The findings support the hypothesis that patients suffering from dystonias without persistent abnormalities in the basal ganglia may have dysfunction in nigrotectal system.

The projected activity in this project is publication of the research findings and an analysis of a database on control values of rCMRglu, considering various factors (i.e., season of year, age, length of anesthesia during preparation of rats) which may influence cerebral glucose metabolism.

## Publications

Wise, P.M., Walovitch, R.C., Cohen-Becker, I.R., Weiland, N.G. and London, E.D.: Effect of age on the circadian rhythm of local cerebral glucose utilization in ovariectomized rats. J. Neurosci. 7: 3469-3473, 1987.

Wise, P.M., Cohen, I.R., Weiland, N.G. and London, E.D.: Aging alters the circadian rhythm of glucose utilization in the suprachiasmatic nucleus. Proc. Natl. Acad. Sci. U.S.A. 85: 5305-5309, 1988.

Cadet, J.L., Della Puppa, A. and London, E.D.: Involvement of nigrotectal-reticulospinal pathways in the iminodipropionitrile (IDPN) model of spasmodic dyskinesias: A 2-deoxy-D-[1-<sup>14</sup>C]glucose study in the rat. Brain Res., In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00210-03 NPL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effects of Chronic Drug Abuse on Lymphoid and Cerebral Receptors

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.D. London Chief NPL, ARC, NIDA

Others: A.S. Kimes Visiting Scientist NPL, ARC, NIDA  
W.J. Smith Research Chemist BPB, USAMRICD

COOPERATING UNITS (if any)

USAMRICD, Aberdeen Proving Ground, MD

LAB/BRANCH

Neuropharmacology Laboratory/Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.30

PROFESSIONAL:

0.20

OTHER:

0.10

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Intravenous drug abusers show an abnormally high rate of human immunodeficiency virus (HIV) infection, suggesting that chronic exposure to abused substances may alter immune function. Since morphine is commonly abused by intravenous injection, the effect of chronic treatment with this opioid was measured using three techniques: (1) flow cytometry and monoclonal antibodies to detect relative numbers of subpopulations of peripheral blood T-lymphocytes; (2) the response of splenocytes to mitogen stimulation; and (3) densities and affinities of splenocyte receptors for neuroactive substances which may be involved in immune function.

Morphine-treated mice had fewer circulating T-lymphocytes (helpers and suppressor/cytotoxic) than concurrent controls. The effect was dose-dependent and was correlated with lower spleen/body weight ratios and white cell counts, but was not blocked by treatment with the opioid antagonist naltrexone. The effect of morphine on T-lymphocytes occurred within 24 hours of initiation of treatment. Oxymorphone caused a similar effect. Morphine treatment did not affect mitogen-stimulated lymphocyte proliferation.

**Effects of Chronic Drug Abuse on Lymphoid and Cerebral Receptors**

Scatchard analysis and displacement studies of sigma receptors in mouse splenocytes demonstrated binding characteristics that were similar, but not identical, to those of sigma receptors in other species. Preliminary results suggested a reduction in the number of sigma binding sites on mouse splenocytes may be associated with chronic morphine treatment.

This work suggests that morphine may compromise immunocompetency and that the use of opioids by intravenous drug abusers may increase the incidence of infection subsequent to exposure to bacterial and viral agents (e.g., HIV).

Projected studies will focus of chronic treatments with other drugs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>	PROJECT NUMBER ZO1 DA00212-04 NPL
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PERIOD COVERED  
 October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
**Studies of Multiple Opioid Receptor Subtypes**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: T.-P. Su	Pharmacologist	NPL, ARC, NIDA
Others: E.D. London	Chief	NPL, ARC, NIDA
D.B. Vaupel	Pharmacologist	NPL, ARC, NIDA
C. Ori	Visiting Fellow	NPL, ARC, NIDA
X.Z. Wu	Visiting Associate	NPL, ARC, NIDA
P.R. Oeltgen	Associate Professor	U of Kentucky
D.S. Bruce	Professor	Wheaton College

COOPERATING UNITS (if any)

University of Kentucky, Wheaton College

LAB/BRANCH  
 Neuropharmacology Laboratory/Neuroscience Branch

SECTION

INSTITUTE AND LOCATION  
 Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.65	PROFESSIONAL: 0.65	OTHER: 0.00
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CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects     
 ☐ (b) Human tissues     
 ☒ (c) Neither

☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Three clinically widely-used analgesics (meperidine, propoxyphene and methadone) were found to interact mainly with mu and sigma opioid receptors. Rats which were supersensitive to naltrexone in suppressing a food-seeking behavior were found to have increased sigma receptors (21%) and reduced kappa receptor (37%) in the midbrain and reduced sigma receptors (21%) in cortex. Mu receptors were not changed. Multiple opioid receptors were found to play interesting roles in animal hibernation. Sigma receptors may involve induction of hibernation since sigma, but not mu and kappa ligands, induced summer hibernation in ground squirrels. Mu and kappa receptors, however, may be important for arousal from hibernation.

In studies of kappa receptors in human neuropsychopathological conditions, it is important to know the biochemical stability of kappa receptors under storage conditions simulating those to which human autopsy material is subjected. A study using guinea pig brains demonstrated an extraordinary stability of kappa receptors).



### Studies of Multiple Opioid Receptor Subtypes

One possible mechanism of action of anesthetics is alteration of neurotransmitter receptor binding. Thus, the effects of nitrous oxide ( $N_2O$ ) and halothane were examined on mu and kappa receptors.  $N_2O$  increased the  $K_d$  values for mu and kappa receptors, and decreased the  $B_{max}$  of kappa binding. Halothane increased the  $K_d$  for mu receptors, but decreased the  $K_d$  for kappa receptors with a concomitant decrease in the  $B_{max}$ . Thus, volative anesthetics affect mu and kappa opioid receptors.

The effects of a kappa peptide BW942C on urine output were examined in humans, rats, and squirrel monkeys. BW942C bound to mu, kappa and sigma receptors, was diuretic at low doses, and antidiuretic at higher doses. The antidiuretic effect was antagonized by low doses of naltrexone; however, the less efficacious diuretic effect of the kappa drug, U50488, was antagonized by high doses of naltrexone. The results suggest that BW942C is a partial kappa agonist and a mu agonist.

### Publications

Bruce, D.S., Cope, G.W., Elam, T.R., Ruit, K.A., Oeltgen, P.R. and Su, T.-P.: Opioids and hibernation: I. Effects of naloxone on bear HIT's depression of guinea pig ileum contractility and on induction of summer hibernation in ground squirrel. Life Sci. 41: 2107-2113, 1987.

Oeltgen, P.R., Welborn, J.R., Nuchols, P.A., Spurrier, W.A., Bruce, D.S. and Su, T.-P.: Opioids and hibernation: II. Effects of kappa opioid U69593 on induction of hibernation in summer-active ground squirrels by "hibernation induction trigger" (HIT). Life Sci. 41: 2107-2113, 1987.

Ori, C., Su, T.-P., Weissman, A.D. and London, E.D.: Extraordinary postmortem stability of kappa opioid receptors in guinea pig brain. J. Pharm. Pharmacol. 39: 951-954, 1987.

Oeltgen, P.R., Nuchols, P.A., Nilekani, S.P., Spurrier, W.A. and Su, T.-P.: Further studies on opioids and hibernation: Delta opioid receptor ligand selectively induced hibernation in summer-active ground squirrels. Life Sci., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  ZO1 DA00217-04 NPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Structures and Activities of Semirigid Nicotinic Agonists		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: C.E. Spivak  Others: J.A. Waters T.M. Gund K. Magleby R. Aronstam	Pharmacologist  Chemist Chemist Biophysicist Biochemist	NPL, ARC, NIDA  NIH New Jersey Inst. Tech. University of Miami Med. College of Georgia
COOPERATING UNITS (if any)  NIH, New Jersey Institute of Technology, University of Miami, Medical College of Georgia		
LAB/BRANCH Neuropharmacology Laboratory/Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.70	PROFESSIONAL: 0.70	OTHER: 0.00
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>The objective of this project is to elucidate the molecular mechanisms of drug recognition. A model receptor, the nicotinic receptor in voluntary muscle, was used since more is known about this receptor than any other, and because it directly transduces the recognition of nicotinic agonists into electrical current through the ion channel that it gates. In the course of this study, over 15 new agonists have been synthesized (by Waters and Spivak), modeled (by Gund), and assayed for potency in the interosseal muscle from the frog (by Spivak). Further insight into the agonist's actions was obtained by electrophysiological experiments, especially the patch clamp technique, which makes it possible to record the electrical currents through single ion channels.</p> <p>In the past year, the patch clamp data for isoarecolone methiodide (the most potent agonist) and for dihydroisoarecolone methiodide were reviewed, event by event, and analyzed (with assistance from Dr. K. Magleby). The data were best-fit by three open and five shut states of the receptor, more states than are generally recognized. The kinetics of the open states clearly differed between the two agonists, but the shut states were indistinguishable.</p>		

### Structures and Activities of Semirigid Nicotinic Agonists

This finding suggests that the receptor distinguishes between these two agonists, only when it is occupied and the ion channel is open, not in the binding step, as one might expect.

The sequence of channel events may provide information on how the kinetic states are interconnected. To this end, autocorrelation and contingency analyses are being implemented. Preliminary results indicate that the three open states are connected to the shut states by at least two (probably three) "gateway" states. The results will now be prepared for publication.

### Publications

Waters, J.A., Spivak, C.D., Hermsmeier, M., Yadav, J.S., Liang, R.F. and Gund, T.M.: Synthesis: Pharmacology and molecular modeling studies of semirigid, nicotinic agonists. J. Med. Chem. 31: 545-554, 1988.

Spivak, C.E., Yadav, J.S., Shang, W.C., Hermsmeier, M. and Gund, T.M.: Carbamyl analogues of potent nicotinic agonists: Pharmacology and computer-assisted molecular modeling study. J. Med. Chem., In press.

McManus, O.B., Weiss, D.S., Spivak, C.E., Blatz, A.L. and Magleby, K.L.: Fractal models are inadequate for the kinetics of four different ion channels. Biophys. J., In press.

Spivak, C.E., Waters, J.A. and Aronstam, R.S.: Binding of semirigid, cholinergic agonists to nicotinic and muscarinic receptors. Mol. Pharmacol., In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER ZO1 DA00218-01 NPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cerebral Metabolic Effects of GP-120 and Proposed Treatments for HIV Infection		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.D. London	Chief NPL, ARC, NIDA
Others:	A.S. Kimes B. Tabakoff J. Szabo	Visiting Scientist Director, Intramural Research Visiting Fellow NPL, ARC, NIDA NIAAA NIAAA
COOPERATING UNITS (if any) Intramural Research Program, NIAAA, Bethesda, MD		
LAB/BRANCH Neuropharmacology Laboratory/Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.45	0.25	0.20
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>Infection by human immunodeficiency virus (HIV) sometimes accompanies dementia. GP-120, the HIV viral envelope glycoprotein, binds specifically to brain membranes and T-lymphocytes, as does peptide T, a proposed treatment for HIV infection. Work in other laboratories has demonstrated that peptide T binds to cerebral receptors for vasoactive intestinal peptide (VIP), and protects against GP-120-induced neurotoxicity <u>in vitro</u>. The present project was initiated to accomplish the following objectives: (1) to compare distribution of peptide T action with that of vasoactive intestinal peptide; (2) to determine if GP-120 can affect brain function in the absence of viral infection; (3) to determine if peptide T can block the potential effects of GP-120. The initial approach to accomplish these goals involved treating rats with intracerebroventricular (icv) injections of GP-120, peptide-T, and VIP to determine the distribution of effects on the regional cerebral metabolic rate for glucose (rCMRglu).</p> <p>Rats received one of the following treatments by icv cannula 5 min. before the injection of 2-deoxy-D-[1-<sup>14</sup>C]deoxyglucose, peptide T, VIP, or vehicle (2 pl of artificial cerebrospinal fluid). Rates of rCMRglu were determined autoradiographically in 35 brain regions.</p>		

**Cerebral Metabolic Effects of GP-120 and Proposed Treatments for HIV Infection**

Neither the effects of peptide T, nor those of VIP, followed closely the distribution of VIP receptors in the rat brain. Peptide T tended to reduce rCMRglu in a few subcortical areas, which exhibited no effects associated with VIP. In contrast, VIP tended to stimulate rCMRglu in the telencephalon

Ongoing work is directed at testing the effect of GP-120 on brain metabolism and its potential interactions with peptide T.

### 3. Neurobiology Laboratory — Chief, Errol B. DeSouza, Ph.D.

#### Overview

The Laboratory of Neurobiology is a newly formed Laboratory which conducts research on the neurobiological underpinnings of drug abuse and addiction. At present, the Laboratory has three major areas of research which include: (1) the study of the neuroendocrine aspects of addiction with a focus on stress, hypothalamic peptides and drugs of abuse; (2) the study of the pharmacological and neurotoxic effects of drugs of abuse; and (3) the study of the interactions of the brain-neuroendocrine-immune axis and its related peptides, hormones, lymphokines, and monokines. In addition, a program is being developed to examine biochemical and behavioral factors related to the vulnerability for drug abuse and drug dependence. The Laboratory utilizes a multifaceted approach which includes biochemical, cellular, pharmacological and neuroanatomical techniques to investigate the problems outlined above.

Stress is a key factor which plays a major role in both the initiation and maintenance of drug abuse. Furthermore, stress produces profound and sustained neurochemical changes in the body and interacts in a complex manner with psychotropic and addictive drugs. A major effort of the Laboratory has been directed at understanding the basic mechanisms regulating stress responses. Corticotropin-releasing factor (CRF) is a critical hormone involved with stress responses. In addition to its role in regulating stress responses via the endocrine system, recent evidence suggests that CRF may act as a neurotransmitter in brain and function as an integrator of the overall stress response in the body. An important ongoing project is to establish CRF as a bona fide neurotransmitter in the CNS. Biochemical, cellular, pharmacological and neuroanatomical studies have been utilized to study the characteristics and distributions of CRF and its receptors as well as the second messenger systems through which CRF produces its many effects, and to establish molecular neurobiological techniques by which to identify specific intracellular messenger RNA for CRF.

To date, investigators in the Laboratory have identified high affinity binding sites for CRF in brain which are distributed throughout the central nervous system (CNS). In addition, the second messenger system through which CRF produces its effects in brain has been identified as involving stimulation of adenylate cyclase activity. Biochemical studies have identified the ligand binding subunits of CRF receptors in brain and anterior pituitary of a number of species by chemical affinity cross-linking techniques. Moreover, a combination of immunocytochemical, molecular biological and receptor autoradiographic techniques have been used to demonstrate that CRF is a major transmitter in the olivocerebellar pathway in a variety of species including humans. The production of neuroanatomical maps for CRF as well as mRNA for CRF and CRF receptors has provided the basis for subsequent studies examining the effects of various drugs of abuse that modulate CRF neurotransmission and stress responses. It is anticipated that the data generated from these studies will be helpful in elucidating the basic mechanisms underlying stress responses and the interactions between stress and drugs of abuse.



To further investigate the role of CRF in brain, changes in various CRF markers in neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease and progressive supranuclear palsy, have been examined. Initial studies have shown that in Alzheimer's disease the concentrations of CRF-like immunoreactivity are reduced and that there are reciprocal increases in CRF receptor binding in affected cerebrocortical areas. Decreases in CRF-like immunoreactivity similar to those described for Alzheimer's disease were also seen in patients who died of Parkinson's disease and progressive supranuclear palsy. In contrast, patients who died of Huntington's disease did not show decrements in CRF-like immunoreactivity in the cerebral cortex, but exhibited significant decreases in CRF content in the caudate/putamen. More recently, abnormalities in CRF neurons have been demonstrated in patients who died of Alzheimer's disease in that CRF-like immunoreactivity was localized to senile plaques. These results strongly support a neurotransmitter role for CRF in brain and suggest a possible role for CRF in the pathophysiology of various neurodegenerative disorders. In addition, they also suggest a role for CRF in brain in processes involving cognition, short-term memory and movement.

The psychotomimetic agent, 3,4-methylenedioxymethamphetamine (MDMA), has recently been the focus of a great deal of attention since it represents one of the most popular members of the class of abused substances known as designer drugs. A major research focus of the Laboratory has been to study the neurochemical mechanisms through which MDMA, 3,4-methylenedioxyamphetamine (MDA), and related amphetamine derivatives produce their psychotomimetic and neurotoxic effects. With regard to the psychotomimetic effects, the Laboratory has demonstrated that MDMA and MDA have highest affinity for 5-HT<sub>2</sub> serotonin receptors in brain; these receptors have been shown to be the site of action through which a variety of amphetamine derivatives produce their hallucinogenic effects. Studies carried out in rats and monkeys have demonstrated that chronic administration of MDA and MDMA results in widespread and long-term destruction of serotonin nerve terminals in brain.

In addition, other related investigations have revealed that MDMA is more potent, on a mg/kg basis, in destroying serotonin terminals in primates than in rodents. Although regeneration of serotonin neurons occurs in brain, the recovery requires a protracted period of time in rat. Notably, a marked 25% reduction was observed even six months after treatment with MDMA. Again, rhesus monkeys appeared to be more susceptible to the effects of MDMA, with decreases in the cerebrospinal (CSF) concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), and decreases (greater than 70%) in brain concentrations of a variety of serotonergic markers evident even at four months after a short-term treatment.

With respect to ameliorating these effects, importantly the neurotoxic effects of MDA and MDMA in rats could be prevented by pretreatment with a serotonin uptake blocker. Moreover, autoradiographic and immunocytochemical studies have demonstrated that the destructive effects of these compounds on serotonin neurons in brain were not diffuse, but were rather limited to certain brain areas. Specifically, MDA and MDMA appeared to

destroy serotonin terminals in ascending pathways, while serotonin neurons in descending pathways, axons of passage, and serotonin cell bodies appeared to be relatively spared. Overall, these studies examining the effects of MDA and MDMA in rodents and primates have elucidated the neurotoxic effects of these compounds on serotonin neurons in brain and are strongly suggestive of their potential neurotoxic hazard in humans.

In addition to these compounds, a variety of amphetamine derivatives as well as structurally unrelated compounds with a pharmacological profile similar to amphetamine are currently used to treat certain psychiatric disorders. These drugs include fenfluramine which is used for the treatment of obesity and infantile autism. Another widely prescribed amphetamine-related drug is methylphenidate (Ritalin) which is used for the treatment of attention deficit disorders in children and adolescents. Methylphenidate abuse has also been reported in adults. The compound has not been found to produce long-term neurotoxic effects in rodents. In contrast, short-term fenfluramine treatment was associated with dose-dependent decreases in a variety of serotonergic markers (serotonin levels, 5-HIAA) and serotonin uptake sites in a variety of brain regions; no major effects were noted on catecholamine markers. Immunocytochemical studies confirmed the neurochemical data which demonstrate that the neurotoxic effects of fenfluramine result in profound reduction in fine-caliber serotonin-immunoreactive fibers and terminals, with no major effects on cell bodies.

Dopamine and other brain monoamines have been implicated in mediating the reinforcing properties and behavioral effects of cocaine. While the effects of cocaine administration have been examined relative to the concentration of brain monoamines, the reports in the literature are conflicting. Furthermore, some recent data suggest that cocaine administration may produce neurotoxic effects on brain dopaminergic systems. In preliminary studies in this Laboratory examining the effects of cocaine administration (20 mg/kg twice daily for eight days), no marked or consistent changes were observed in the concentrations of dopamine or its metabolites in brain regions, such as the frontal cerebral cortex and hypothalamus at timepoints up to 48 days following the treatment regimen. Cocaine administration appeared to produce more consistent effects on hypothalamic serotonin which has been implicated in the neuroendocrine effects of the drug. Neuroanatomical studies and more detailed neurochemical studies are currently being carried out to assess the effects of cocaine on brain monoamine transmission.

Intravenous drug abusers are at higher risk for viral infections such as AIDS. While the disease is propagated through the use of contaminated needles, the potent immunosuppressant effects of a variety of substances of abuse, including opioids, may explain, at least in part, the increased progression of the disease in drug addicts. Moreover, a variety of CNS functions appear to be affected in AIDS patients. The presence of neurotransmitters and receptors which are common to the immune, endocrine and central nervous systems suggests that these three systems may interact in a coordinated fashion. Since phencyclidine (PCP) and sigma opioids as well as chronic stress have been demonstrated to cause immunosuppression and to alter a



variety of endocrine and CNS functions, the potential role of sigma drugs and CRF in modulating immune function has been examined.

In addition, attention has been given to investigating the role of interleukin-1 (IL-1), a cytokine which is a key mediator of the immune response to AIDS infection, stress, and antigenic challenge. Sigma, CRF and IL-1 receptors were identified in immune, endocrine and CNS tissues. In the immune system, CRF receptors were found in mouse spleen, primarily in splenic macrophages. Also, sigma receptors were identified in human peripheral blood leukocytes and in rat spleen. IL-1 receptors were localized in mouse spleen, primarily in lymphocytes. The results of these studies suggest that PCP exerts its immunomodulatory influence via sigma receptors, and that endogenous sigma ligands, if in fact, they exist, may play a role in immune function. Further, the data suggest the importance of stress and the key players in the stress response, such as CRF and IL-1, in modulating immune function. In addition, these studies have identified IL-1 receptors in brain which may explain partially the behavioral and CNS actions that are seen in AIDS patients in which IL-1 concentrations are dramatically altered.

#### Summary of Ongoing Research

##### A. Corticotropin-Releasing Factor (CRF) as a Stress Neurotransmitter in the Central Nervous System

CRF is a critical hormone involved in stress responses and recent evidence suggests that CRF is a neurotransmitter in brain. Current and future studies are aimed at characterizing CRF binding sites at a molecular level and examining the effects of a variety of treatments on these receptors. More specifically, a variety of chemical cross-linking techniques are used to study the molecular composition of the CRF receptors and studies are being initiated to purify the CRF receptor in an attempt to sequence the protein and clone the receptor. In addition, attempts are being made to examine the modulation of CRF receptors both in vivo and in vitro. These studies include evaluating the effects of chronic treatment with antidepressants and drugs of abuse, such as benzodiazepines, cocaine, opioids, and amphetamines, on a variety of CRF markers in the CNS and anterior pituitary. Moreover, studies are underway to examine the effects of acute and chronic stress on CRF receptors in the brain and the pituitary. Previous work has established the presence of CRF receptors in dissociated brain cultures and current studies are examining the effects of a variety of drugs on alterations in these binding sites. Studies are also underway to further elucidate the neuroanatomical substrates underlying the actions of CRF in brain by examining the effects of CRF on glucose utilization, an index of cerebral function.



## **B. The Role of Transmitters and Their Receptors in Human Neuropsychiatric Disorders in Neurodegenerative Diseases**

Changes in specific neurotransmitters and their receptors play a key role in the pathophysiology of various neuropsychiatric disorders and neurodegenerative diseases. The ongoing studies are aimed at examining the molecular and biochemical characteristics of CRF receptors in brain tissue from patients who have died of Alzheimer's disease and age-matched controls. Specifically, plans are to use cross-linking techniques to determine whether the receptors in Alzheimer's disease have the same molecular components as "normal" CRF receptors and, further, to assess whether CRF receptors in Alzheimer's disease are indeed functional, as indicated by alterations in second messenger activity. Other studies are aimed at examining changes in CRF content and its receptors, sigma receptors, PCP receptors, and dopamine receptors in human postmortem tissue obtained from schizophrenic patients, depressed patients, Alzheimer's disease patients, and drug addicts.

## **C. Pharmacological and Neurotoxic Effects of MDA and MDMA**

The designer drugs, MDA and MDMA, have potent, long-lasting, neurotoxic effects in brain. In addition, MDA, MDMA and related amphetamine derivatives produce a variety of behavioral effects through actions in the CNS. The goals of this project are to further assess the neurotoxic actions of these drugs and to determine the receptors in brain through which these drugs may produce the neurotoxic actions and behavioral effects. Studies are currently being conducted to examine the mechanisms responsible for the neurotoxic effects of the drugs. In addition, neuroanatomical studies are being carried out to determine the serotonergic pathways that are affected and the long-term consequences of serotonin depletion in the affected pathways. Moreover, studies are being carried out to identify MDA and MDMA binding sites in brain and to develop methods for the detection of these compounds in the periphery and in the CNS.

## **D. Neurochemical, Neuroendocrine and Neurotoxic Effects of Cocaine and Selected Drugs**

Several drugs that are currently used to treat a variety of psychiatric disorders produce their effects through actions on monoaminergic systems in brain. Studies are currently underway to examine the possible neurotoxic effects of chronic administration of several antidepressant and appetite suppressant drugs that are currently in clinical use, or are being reviewed for approval by the Food and Drug Administration FDA, on monoamine neurons in brain. The focus of these studies will be on fenfluramine, a clinically prescribed appetite suppressant, and on methylphenidate, a drug which is prescribed for treatment of attention deficit disorders. Changes in monoamine transmission will be correlated with changes in

a variety of neuroendocrine parameters with a focus on the measurement of pituitary hormones.

Dopamine and other brain monoamines have been implicated as mediators of the reinforcing properties and behavioral effects of cocaine. Further, recent data suggest that chronic cocaine administration may be neurotoxic to dopaminergic systems in rat brain. Studies are currently underway to examine, in detail, the effects of cocaine administration on changes in various monoamine markers in brain and on several behavioral parameters. The changes in monoamine markers and behavior will be correlated with neuroendocrine changes. In addition, immunocytochemical and autoradiographic studies will be carried out to assess the morphological and neuroanatomical specificity of the effects of cocaine on brain monoamines.

#### E. Interactions Between Brain-Endocrine-Immune Axis

The presence of neurotransmitters and their receptors in the brain, endocrine and immune systems suggests that the three systems may interact in a coordinated fashion. In previous years, work in this Laboratory has identified CRF and sigma receptors in the immune system. More recently, sigma receptors have been identified in very high concentrations in endocrine tissues; these receptors have been shown to have kinetic and pharmacological characteristics similar to those found in brain. In addition, interleukin-1 receptors have been identified in the brain-pituitary-immune axis. Studies which are currently underway will focus on identifying the cell type(s) in the endocrine and immune systems which contain various neurotransmitter receptors and on examining the role the receptors may play in modulating hormone secretion and immune function. The effects of in vivo manipulations, such as application of stress as well as acute and chronic administration of certain drugs of abuse, will be examined on changes in CRF, sigma, PCP and IL-1 receptors in brain, endocrine organs, and immune tissue.

#### Publications

DeSouza, E.B. and Kuyatt, B.L.: Alpha-1 adrenergic receptors in the neural lobe of the rat pituitary: Autoradiographic identification and localization. Endocrinology 120: 2227-2233, 1987.

Yeh, S.Y.: N-debenzylation of pyrilamine and tripeleminamine in the rat: A new metabolic pathway. Drug Metab. Dispos. 15: 466-472, 1987.

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Battaglia, G., Yeh, S.Y. and DeSouza, E.B.: MDMA-induced neurotoxicity: Parameters of degeneration and recovery of brain serotonin neurons. Pharmacol. Biochem. Behav. 29: 269-274, 1988.

Battaglia, G., Brooks, B.L., Kulsakdinun, C. and DeSouza, E.B.: Pharmacologic profile of 3,4-methylenedioxymethamphetamine (MDMA) at various brain recognition sites. Eur. J. Pharmacol. 149: 159-163, 1988.

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DeSouza, E.B., Webster, E.L. and Grigoriadis, D.E.: Corticotropin-releasing factor (CRF) receptors in the brain pituitary immune axis. Corticotropin-Releasing Factor Symposium, Chapel Hill, NC, 1988.

DeSouza, E.B. and Wong, D.F.: Receptor imaging: Applications in psychiatry. American Psychiatric Association Meeting, Montreal, Canada, 1988.

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Contrera, J.F., Battaglia, G., Zaczek, R. and DeSouza, E.B.: Fenfluramine neurotoxicity: Selective degeneration and recovery of brain serotonin neurons. Soc. Neurosci. Abstr., 1988.

Appel, N.M. and DeSouza, E.B.: Fenfluramine selectively destroys serotonin terminals in brain: Immunocytochemical evidence. Soc. Neurosci. Abstr., 1988.

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Culp, S., Zaczek, R. and DeSouza, E.B.: Incorporation of <sup>3</sup>H-methylenedioxymphetamine (MDA) into rat brain synaptosomes. Soc. Neurosci. Abstr., 1988.

Battaglia, G., Sharkey, J., Kuhar, M.J. and DeSouza, E.B.: Neuroanatomical specificity of MDA- and MDMA-induced degeneration of serotonin neurons in rat brain. Soc. Neurosci. Abstr., 1988.

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Yousif, M., Battaglia, G., DeSouza, E.B., Glennon, R.A.: Sigma receptors: A putative site of action of MDMA (3,4-methylenedioxymethamphetamine) and related analogs. Soc. Neurosci. Abstr., 1988.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00300-01 NBL *Z01 DA00010-02 NEI
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Metabolism of Tripeleennamine and Pyrilamine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: S.Y. Yeh Pharmacologist NBL, ARC, NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH  
Laboratory of Neurobiology, Neuroscience Branch, \*Reassigned from MPL June 88

SECTION

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.20	PROFESSIONAL: 0.20	OTHER: 0.00
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CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Tripeleennamine, an antihistamine, has been abused in combination with pentazocine, a narcotic agonist/antagonist. The purpose of this study is to determine the effect of pentazocine on the urinary metabolic profile of tripeleennamine.

The major metabolite of tripeleennamine in rats was found to be 4'-hydroxytripeleennamine in both free and conjugated forms. After administration of drug, urine was collected, hydrolyzed with gluculase and extracted with benzene-isopropanol. Extracts were analyzed by thin layer chromatography, gas chromatography, and gas chromatography/mass spectrometry. In man, free and conjugated alpha-hydroxytripeleennamine were the major metabolites of tripeleennamine. Concentrations of tripeleennamine, N-glucuronide-conjugated tripeleennamine and total (free plus conjugated) alpha-hydroxytripeleennamine in the 24-hour urine were found to be 1.2%, 4.5%, and 23% of the administered dose (100 mg, i.m.), respectively.



### Metabolism of Tripeleennamine and Pyriline

In the 24-hour urine of male rats administered tripeleennamine, the amount of tripeleennamine and its metabolites, which included 2-(2-dimethylaminoethyl)aminopyridine [#1] in free form, as well as alpha-hydroxytripeleennamine [#2], 4-hydroxytripeleennamine [#3], 2-[4-hydroxy-3-methoxybenzyl-(2-dimethylaminoethyl)-amino]pyridine [#4], and 2-[3-hydroxy-4-methoxybenzyl-(2-dimethylaminoethyl)-amino]pyridine [#5] in conjugated form, were found to be 1.4%, 3.0%, 7.5%, 3.7%, 0.3%, and 0.2% of the administered dose, respectively. A similar pattern was seen in female rats.

In the 24-hour urine of male rats administered pyriline, the amount of pyriline and its metabolites, which included #1 in free form, #3, and 4-hydroxydesmethyltripeleennamine, as well as #4 and #5 in the conjugated form were found to be 1.75%, 0.5%, 25%, 7.5%, and 1.00% of the administered dose, respectively. The respective metabolites in the urine of female rats were 1.2%, 0.5%, 47%, 15%, and 2.0%. These metabolites represented less than 0.5% of the administered dose in the 48 hour urine.

### Publications

Yeh, S.Y.: N-debenzylation of pyriline and tripeleennamine in the rat: A new metabolic pathway. Drug Metab. Dispos. 15: 466-472, 1987.

Yeh, S.Y. and Hsu, F.L.: Quantitative metabolic profile of tripeleennamine and pyriline in the rat. Drug Metab. Dispos. 16: 499-502, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  ZO1 DA000301-01 NBL *ZO1 DA000101-03 MPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Role of Corticotropin-Releasing Factor & Sigma Drugs on Immune Function		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: E.B. DeSouza  Others: E.L. Webster S.E. Wolfe, Jr.	Chief  Graduate Student Staff Fellow	NBL, ARC, NIDA  NBL, ARC, NIDA NBL, ARC, NIDA
COOPERATING UNITS (if any)  None		
LAB/BRANCH Laboratory of Neurobiology, Neuroscience Branch, *Reassigned from MPL June 88		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 1.80	PROFESSIONAL: 0.50	OTHER: 1.30
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input checked="" type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Recent evidence suggests that corticotropin-releasing factor (CRF) and sigma agonists such as phencyclidine (PCP) may have immunomodulatory actions. To evaluate the role of these compounds in regulating immune function, studies have been carried out to identify and localize receptor binding sites in rat and mouse spleen and in human peripheral blood leukocytes (HPBL).</p> <p>With regard to CRF, these studies have identified and characterized specific high affinity receptors in mouse spleen with characteristics similar to those in the brain and pituitary. <sup>125</sup>I-CRF binding to mouse spleen was linear in relation to increasing protein concentration, and was found to be saturable and of a high affinity. In autoradiographic localization studies, CRF binding was found to be localized in red pulp regions of the spleen and a high density of CRF binding sites was observed in macrophages; there was a notable absence of CRF binding in lymphocytes.</p>		

## Role of Corticotropin-Releasing Factor & Sigma Drugs on Immune Function

Subcellular fractionation studies in mouse spleen suggest that CRF receptors are primarily located on splenic macrophages. Sigma receptors were identified and characterized in HPBL and rat spleen; the binding sites had kinetic and pharmacological characteristics similar to those observed for sigma receptors in the brain. The highest density of sigma receptors was found in the rat spleen with lower, but comparable, concentrations in HPBL and rat cerebellum.

In autoradiographic studies, the sigma receptors appeared to be localized primarily on lymphocytes. In addition, preliminary immunological studies have demonstrated the immunosuppressant effects of PCP on natural killer cell activity. Thus, the data demonstrating the presence of CRF and sigma receptors in immune tissue may indicate a physiological role for these endogenous neurotransmitters in modulating immune function. Sigma drugs could conceivably alter the release of lymphokines and monokines and provide additional mechanisms for the central action of these drugs. Also, the receptors in HPBL leukocytes may represent useful peripheral markers in humans for assessing the role of these receptors in the brain.

## Publications

Webster, E.L. and DeSouza, E.B.: Corticotropin-releasing factor receptors in mouse spleen: Identification, autogradiographic localization and regulation by divalent cations and guanine nucleotides. Endocrinology 122: 609-617, 1988.

Wolfe, S.A. Jr., Kulsakdinun, C., Battaglia, G., Jaffe, J.H. and DeSouza, E.B.: Initial identification and characterization of sigma receptors in human peripheral blood leukocytes. J. Pharmacol. Exp. Ther., In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00302-01 NBL  
\*Z01 DA00102-03 MPL

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurotoxic Effects of MDA and MDMA (Ecstasy)

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.B. DeSouza	Chief	NBL, ARC, NIDA
Others:	R. Zaczek	Staff Fellow	NBL, ARC, NIDA
	G. Battaglia	Staff Fellow	NBL, ARC, NIDA
	M.J. Kuhar	Chief	NBL, ARC, NIDA
	S.Y. Yeh	Scientist	NBL, ARC, NIDA
	M. Molliver	Professor	JHU
	T.R. Insel	Scientist	LCS, NIMH

COOPERATING UNITS (if any)

Department of Neuroscience, JHUMI  
Laboratory of Clinical Science, NIMH

LAB/BRANCH

Laboratory of Neurobiology, Neuroscience Branch, \*Reassigned from MPL June 88

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

3.00

PROFESSIONAL:

2.20

OTHER:

0.80

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The goal of the project is, first, to study the neurochemical mechanisms through which 3,4-methylenedioxymphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA) and related amphetamine derivatives produce their neurotoxic effects in the central nervous system and, second, to examine the pharmacologic profile of MDA and MDMA at various brain recognition sites.

Studies have been carried out to examine the effects of subchronic *in vivo* administration of MDA and MDMA on brain monoaminergic systems. Subchronic administration of MDA and MDMA produce selective decreases in both serotonin (5-hydroxytryptamine or 5-HT) and 5-hydroxyindoleacetic acid (5-HIAA), with no major changes in catecholamines in discrete areas of rat and rhesus monkey brain, drastic reductions in 5-HT uptake sites and massive destruction of 5-HT pre-terminals. Following an initial 90% loss of 5-HT uptake sites in rats, the recovery of sites (i.e., neuronal regeneration) occurred over a protracted period of time; a 25% reduction was seen at 6 months after treatment with MDMA.

## Neurotoxic Effects of MDA and MDMA (Ecstasy)

The autoradiographic and immunocytochemical data generated demonstrate that the neurotoxic effects of these compounds on serotonin terminals are not diffuse, but rather are limited to certain brain areas. Notably, the neurotoxic effects of MDA and MDMA in rats could be prevented by pretreatment with a serotonin uptake blocker, citalopram.

The pharmacologic profile of MDA, MDMA and their amphetamine derivatives at various brain receptors was examined using *in vitro* radioligand binding procedures. MDA and MDMA were found to have relatively high affinities for 5-HT uptake sites, 5-HT<sub>1A</sub> receptors, 5-HT<sub>2</sub> receptors, alpha<sub>2</sub>-adrenergic, M-1-muscarinic, and sigma receptors. These compounds have moderate to weak affinities for a variety of other brain recognition sites, including pre- and post-synaptic recognition sites for catecholamines, acetylcholine, opioids and various neuropeptides. In addition, studies in this Laboratory have identified and characterized sites of association of <sup>3</sup>H-MDA and <sup>3</sup>H-MDMA in rat brain synaptosomes.

## Publications

Battaglia, G., Yeh, S.Y., O Hearn, E., Molliver, M.E., Kuhar, M.J. and DeSouza, E.B.: 3,4-Methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) preferentially destroy serotonin terminals in rat brain: Quantification of neurodegeneration by measurement of <sup>3</sup>H-paroxetine-labeled serotonin uptake sites. J. Pharmacol. Exp. Ther. 242: 911-916, 1987.

DeSouza, E.B. and Kuyatt, B.L.: Autoradiographic localization of <sup>3</sup>H-paroxetine-labeled serotonin uptake sites in rat brain. Synapse 1: 488-496, 1987.

Battaglia, G. and DeSouza, E.B.: New perspectives on MDMA. Substance Abuse 3(4): 31-42, 1987.

Battaglia, G. and DeSouza, E.B.: The other side of ecstasy: Neurotoxic effects of MDMA. NIDA Notes 2: 7, 1987.

Battaglia, G., Yeh, S.Y. and DeSouza, E.B.: MDMA-induced neurotoxicity: Parameters of degeneration and recovery of brain serotonin neurons. Pharmacol. Biochem. Behav. 29: 269-274. 1988.

Neurotoxic Effects of MDA and MDMA (Ecstasy)

Publications (Cont'd)

Battaglia, G., Brooks, B.L., Kulsakdirun, C. and DeSouza, E.B.: Pharmacologic profile of 3,4-methylenedioxymethamphetamine (MDMA) at various brain recognition sites. Eur. J. Pharmacol. 149: 159-163, 1988.

O'Hearn, E., Battaglia, G., DeSouza, E.B., Kuhar, M.J. and Molliver, M.E.: Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause ablations of serotonin axon terminals in forebrain: Immunocytochemical evidence. J. Neurosci., In press.

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Battaglia, G., Zaczek, R. and DeSouza, E.B.: MDMA effects in Brain: Pharmacologic Profile and Evidence of Neurotoxicity from Neurochemical and Autoradiographic Studies. In Peroutka, S.J. (Ed.): MDMA: "Ecstasy" and/or Human Neurotoxin? Boston, MA, Kluwer Academic Publishers, In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  ZO1 DA00303-01 NBL *ZO1 DA00103-03 MPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Corticotropin-Releasing Factor in Human Neurodegenerative Diseases</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	<b>E.B. DeSouza</b>  Others: D.L. Price P.J. Whitehouse R. Powers L. Walker W.W. Vale	<b>Chief</b>  Professor Associate Professor Associate Professor Associate Professor Scientist  JHU JHU JHU JHU Salk Institute
COOPERATING UNITS (if any)  Neuropathology Laboratory, JHU; Clayton Foundation Laboratories for Peptide Biology, The Salk Institute, San Diego, CA		
LAB/BRANCH Laboratory of Neurobiology, Neuroscience Branch, *Reassigned from MPL June 88		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 2.00	PROFESSIONAL: 1.50	OTHER: 0.50
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input checked="" type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>             The goal of this project is to study the role of brain corticotropin-releasing factor (CRF) in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and progressive supranuclear palsy. Initially, this project examined brain tissue from individuals with Alzheimer's disease or control subjects for pre- and post-synaptic markers for CRF. In tissue from individuals with Alzheimer's disease, the concentrations of CRF-like immunoreactivity were found to be reduced; moreover, there were reciprocal increases in CRF receptor binding in affected cerebral cortical areas. These changes were significantly correlated with decrements in choline acetyltransferase activity. Decreases in CRF-like immunoreactivity similar to those described for Alzheimer's disease were also seen in patients who died of Parkinson's disease and progressive supranuclear palsy. In contrast, patients who died of Huntington's disease did not show decrements in CRF-like immunoreactivity in the cerebral cortex, but showed significant decreases in CRF-like immunoreactivity in the caudate/putamen. More recently, abnormalities have been demonstrated in CRF-like immunoreactive neurons in patients who died of Alzheimer's disease in that the CRF-like immunoreactivity was localized to senile plaques.           </p>		

## Corticotropin-Releasing Factor in Human Neurodegenerative Diseases

These results strongly support a neurotransmitter role for CRF in brain and demonstrate, for the first time, a modulation of central nervous system (CNS) CRF receptors associated with altered CRF content. These observations further suggest a possible role of CRF in the pathophysiology of various neurodegenerative disorders. Thus, future therapies directed at increasing CRF levels in brain may prove useful for the treatment of Alzheimer's disease and other neurodegenerative disorders.

### Publications

Whitehouse, P.J., Vale, W.W., Zweig, R.M., Price, D.L. and DeSouza, E.B.: Reductions in corticotropin-releasing factor-like immunoreactivity in cerebral cortex in Alzheimer's disease, Parkinson's disease and progressive supranuclear palsy. Neurology 37: 905-909, 1987.

Powers, R.E., Walker, L.C., DeSouza, E.B., Vale, W.W., Struble, R.G., Whitehouse, P.J. and Price, D.L.: Evidence for structural abnormalities of corticotropin-releasing factor neurons in Alzheimer's disease. Synapse 1: 405-410, 1987.

DeSouza, E.B., Whitehouse, P.J., Price, D.L. and Vale, W.W.: Abnormalities of CRH in Alzheimer's disease and other human disorders. New York Acad. Sci. 512: 237-247, 1987.

DeSouza, E.B., Whitehouse, P.J., Price, D.L., Folstein, S.E. and Vale, W.W.: Corticotropin-releasing hormone (CRH) is decreased in the basal ganglia in Huntington's disease. Brain Research 437: 355-359, 1987.

DeSouza, E.B., Bissette, G., Whitehouse, P.J., Price, D.L., Vale, W.W. and Nemeroff, C.B.: Role of corticotropin-releasing factor (CRF) in neurodegenerative diseases. In DeSouza, E.B. and Nemeroff, C.B. (Eds.): Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, Boca Raton, FL, CRC Press, In press.

DeSouza, E.B.: CRH defects in Alzheimer's and other neurologic diseases. Hosp. Pract., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>	PROJECT NUMBER  ZO1 DA00304-01 NBL *ZO1 DA00104-03 MPL
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PERIOD COVERED  
 October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
**Corticotropin-Releasing Factor as a Stress Neurotransmitter in the CNS**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.B. DeSouza	Chief	NBL, ARC, NIDA
Others: D.E. Grigoriadis	Postdoctoral Fellow	NBL, ARC, NIDA
G. Battaglia	Staff Fellow	NBL, ARC, NIDA
D.L. Price	Professor	JHU
R. Powers	Professor	JHU
L. Walker	Professor	JHU
L.P. Kapcala	Professor	Univ. of MD

COOPERATING UNITS (if any)

Neuropathology Laboratory, JHU School of Medicine, Baltimore, MD  
 Department of Medicine, University of Maryland, Baltimore, MD

LAB/BRANCH  
 Laboratory of Neurobiology, Neuroscience Branch, \*Reassigned from MPL June 88

SECTION

INSTITUTE AND LOCATION  
 Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 2.50	PROFESSIONAL: 1.80	OTHER: 0.70
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CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither  
     ☐ (a1) Minors  
     ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Corticotropin-releasing factor (CRF) is a critical hormone involved with stress responses. In addition to its role in regulating stress responses via the endocrine system, recent evidence suggests that CRF may act as a neurotransmitter in brain to integrate the overall response of the body to stress. To provide additional evidence for CRF as a neurotransmitter in brain, studies have been carried out to identify receptor binding sites for CRF in the CNS. Biochemical, cellular, pharmacological and neuroanatomical studies have been utilized to study the characteristics and distributions of CRF and its receptors, as well as the second messenger systems through which CRF produces its many effects, and to establish molecular neurobiological techniques to identify specific intracellular messenger RNA for CRF. High affinity binding sites have been identified for CRF in brain which are distributed throughout the central nervous system (CNS). The anatomical distribution of these sites corresponds with the immunocytochemical distribution of CRF-containing terminals and the pharmacological sites of action of CRF in brain.



## Corticotropin-Releasing Factor as a Stress Neurotransmitter in the CNS

In addition, studies have demonstrated that CRF stimulates adenylate cyclase activity in rat CNS. In biochemical studies, the ligand binding subunits of CRF receptors have been identified in brain and anterior pituitary of a number of species using chemical affinity cross-linking techniques. Moreover, using a combination of immunocytochemical and receptor autoradiographic techniques, it has been shown that CRF is a major transmitter in the olivocerebellar pathway in a variety of species, including humans. Also, *in situ* hybridization histochemistry has been employed to localize intracellular messenger RNA for CRF in rodent, monkey, and human brain. The production of neuroanatomical maps for CRF, as well as mRNA for CRF and CRF receptors has set the basis for subsequent studies designed to examine the effects of various drugs that modulate CRF neurotransmission and stress responses. These data should be helpful in explaining the mechanisms underlying stress responses.

## Publications

DeSouza, E.B.: Corticotropin-releasing factor receptors in the rat central nervous system: Characterization and regional distribution. J. Neurosci. 7: 88-100, 1987.

Powers, R.E., DeSouza, E.B., Walker, L.C., Price, D.L., Vale, W.W. and Young III W.S.: Corticotropin-releasing factor as a transmitter in the human olivocerebellar pathway. Brain Res. 415: 347-352, 1987.

Battaglia, G., Webster, E.L. and DeSouza, E.B.: Characterization of corticotropin-releasing factor (CRF) receptor-mediated in adenylate cyclase activity in rat brain. Synapse 1: 572-581, 1987.

Grigoriadis, D.E. and DeSouza, E.B.: The brain corticotropin-releasing factor (CRF) receptor is of lower apparent molecular weight than the CRF receptor in anterior pituitary: Evidence from chemical cross-linking studies. J. Biol. Chem. 263: 10927-10931, 1988.

Kapcala, L.P. and DeSouza, E.B.: Characterization of corticotropin-releasing factor receptors in dissociated brain cell cultures. Brain Res. 456: 159-167, 1988.

Insel, T.R., Battaglia, G., Fairbanks, D.W. and DeSouza, E.B.: The development of brain receptors for corticotropin-releasing factor and their functional association with adenylate cyclase. J. Neurosci., In press.

Corticotropin-Releasing Factor as a Stress Neurotransmitter in the CNS

Publications (Cont'd)

Bell, J.A. and DeSouza, E.B.: Functional corticotropin-releasing factor (CRF) receptors in the neonatal rat spinal cord: Evidence from autoradiographic and electrophysiological studies. Peptides, In press.

Cummings, S., Young III, W.S., Bishop, G., DeSouza, E.B. and King, J.S.: Distribution of corticotropin-releasing factor in the cerebellum and precerebellar nuclei of the opossum: A study utilizing immunohistochemistry, in situ hybridization histochemistry and receptor binding. J. Comp. Neurol., In press.

Insel, T.R., Battaglia, G. and DeSouza, E.B.: Brain Corticotropin-Releasing Factor and Development. In Zinder, O. and Bresnitz, S. (Eds.): Molecular Biology of Stress, New York, NY, Alan R. Liss, In press.

Grigoriadis, D.E. and DeSouza, E.B.: Corticotropin-releasing factor (CRF) receptors in intermediate lobe of the pituitary: Biochemical characterization and autoradiographic localization. Peptides, In press.

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA00305-01 NBL  
\*Z01 DA00113-02 MPL

## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurotoxicity of Selected Drugs to Monoamine Neurons in Brain

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.B. DeSouza	Chief	NBL, ARC, NIDA
Others:	G. Battaglia	Staff Fellow	NBL, ARC, NIDA
	R. Zaczek	Staff Fellow	NBL, ARC, NIDA
	N.M. Appel	Staff Fellow	NBL, ARC, NIDA
	J.C. Contrera	Pharmacologist	FDA

## COOPERATING UNITS (if any)

Food and Drug Administration, Rockville, MD

## LAB/BRANCH

Neurobiology Laboratory, Neuroscience Branch, \*Reassigned from MPL, June 88

## SECTION

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

2.00

## PROFESSIONAL:

1.50

## OTHER:

0.50

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Several drugs that are currently used to treat a variety of psychiatric disorders produce their effects through actions on monoaminergic systems in the brain. While these drugs may produce their beneficial effects through alterations in neurotransmission, the neurotoxic actions of the drugs which occur following repeated use remain poorly assessed. Thus, the goal of this project is to assess the possible neurotoxic effects associated with chronic administration of several antidepressant and appetite suppressant drugs on monoamine neurons in the brain. These drugs include fenfluramine, bupropion (Wellbutrim), methylphenidate (Ritalin), pemoline (Cylert), methamphetamine, bupropion, citalopram and paroxetine. The neurotoxic actions of these drugs would be assessed using neurochemical assays to measure concentrations of the neurotransmitter and its metabolites. In addition, alterations in monoamine uptake site density would be evaluated using radioligand binding techniques. In vitro autoradiography will be used to quantify and visualize changes in uptake site density and immunohistochemistry will be used to visualize monoamine neurons in discrete areas of rat brain. It is hoped that these studies will provide information about: 1) whether the drugs produce neurotoxicity (i.e., degeneration of neurons), and 2) which of the monoaminergic systems may be at risk.



**Neurotoxicity of Selected Drugs to Monoamine Neurons in Brain**

Preliminary studies indicated that short-term fenfluramine treatment caused dose-dependent reductions in a variety of serotonergic markers (5-HT, 5-HIAA and 5-HT uptake sites) in a variety of brain regions; notably, no major effects of the drug were noted on catecholamine markers. Immunocytochemical studies conducted so far confirm the neurochemical data and demonstrate neurotoxic effects of fenfluramine resulting in a profound reduction in fine-caliber 5-HT-immunoreactive fibers and terminals with no major effect on cell bodies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  Z01 DA00306-01 NBL *Z01 DA00100-02 MPL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Neurotransmitter Receptors in the Pituitary Gland		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)  <div style="display: flex; justify-content: space-between;"> <span>PI: E.B. DeSouza</span> <span>Chief</span> <span>NBL, ARC, NIDA</span> </div>		
COOPERATING UNITS (if any) None		
LAB/BRANCH Laboratory of Neurobiology, Neuroscience Branch, *Reassigned from MPL June '88		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: <div style="text-align: center;">0.80</div>	PROFESSIONAL: <div style="text-align: center;">0.40</div>	OTHER: <div style="text-align: center;">0.40</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> (a) Human subjects  <input type="checkbox"/> (a1) Minors  <input type="checkbox"/> (a2) Interviews         </div> <div> <input type="checkbox"/> (b) Human tissues         </div> <div> <input checked="" type="checkbox"/> (c) Neither         </div> </div>		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>Serotonin and catecholamines have been shown to play a major role in regulating pituitary hormone secretion both through effects in brain and direct actions on the pituitary. The goals of this project were to identify, characterize and localize, using <u>in vitro</u> autoradiography, the relative distribution of serotonin-2, dopamine-2, beta-2-adrenergic and alpha-1-adrenergic receptors in the rat pituitary gland. In order to define the role of adrenomedullary catecholamines in regulating the pituitary, studies were carried out to examine the effects of adrenalectomy on beta-2-adrenergic receptors in the rat pituitary gland. The identification of the various receptors described provides further evidence of the importance of these neurotransmitters in regulating pituitary function and demonstrates conditions in which these receptors can be modulated.</p>		

Neurotransmitter Receptors in the Pituitary Gland

Publications

De Souza, E.B.: Modulation of beta-adrenergic receptors in the pituitary gland following adrenalectomy in rats. Neurosci. Lett. 73: 281-287, 1987.

De Souza, E.B. and Kuyatt, B.L.: Alpha-1 adrenergic receptors in the neural lobe of the rat pituitary: Autoradiographic identification and localization. Endocrinology 120: 2227-2233, 1987.

De Souza, E.B.: Localization and modulation of brain and pituitary receptors involved in stress responses. Psychopharmacol. Bull., In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA00307-01 NBL *Z01 DA00012-01 NEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Effects of Cocaine on Monoamines and their Metabolites in Rat Brain		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: S.Y. Yeh  Others: E.B. DeSouza N.M. Appel	Pharmacologist  Chief Staff Fellow	NBL, ARC, NIDA  NBL, ARC, NIDA NBL, ARC, NIDA
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Neurobiology, Neuroscience Branch, *Reassigned from MPL June '88		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:  0.80	PROFESSIONAL:  0.60	OTHER:  0.20
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Dopamine and other brain monoamines have been implicated in mediating the reinforcing properties and behavioral effects of cocaine. While the effects of cocaine administration on the concentration of brain monoamines have been examined, the reports in the literature are conflicting. The purpose of this series of studies is to examine, in detail, the effects of cocaine administration on changes in various monoamine markers in brain as well as on several behavioral parameters. Rats will be injected with cocaine (20 mg/kg, twice daily for eight days, i.p. or s.c.) and the concentrations of norepinephrine, dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid and homovanillic acid, serotonin and its metabolite, 5-hydroxyindoleacetic acid, will be measured in discrete areas of the rat brain (i.e., frontal cerebral cortex, striatum, hippocampus, hypothalamus, midbrain, pons/medulla and spinal cord). In addition, the effects of acute and chronic cocaine administration and withdrawal will be examined on the activity of enzymes (i.e., tyrosine hydroxylase, DOPA decarboxylase, dopamine beta-hydroxylase, and tryptophan hydroxylase) and on the synthesis and turnover rates of dopamine, norepinephrine and serotonin.		

**Effects of Cocaine on Monoamines and Their Metabolites in Rat Brain**

Rats will be sacrificed at various time points (1, 7, 14 and 48 days) following the treatment regimen of cocaine to assess long-term neurochemical changes that may be a consequence of neurotoxic effects of the drug. In addition, immunocytochemical and autoradiographic studies will be carried out to examine the morphological and neuroanatomical specificity of the effects of cocaine on brain monoamines. Preliminary behavioral data demonstrate that the peak locomotor activity induced by repeated cocaine administration was shifted to the left (i.e., occurred at an earlier time) when compared to activity following acute (i.e., single) administration of cocaine. Thus, the neurochemical and neuroanatomical changes in response to chronic cocaine administration are currently being assessed. This is a new project, and there are no publications at this time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00308-01 NBL
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Role of Sigma and Phencyclidine (PCP) Receptors in Endocrine Organs
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.B. DeSouza	Chief
		NBL, ARC, NIDA
Others:	S.E. Wolfe, Jr.	Staff Fellow
		NBL, ARC, NIDA

COOPERATING UNITS (if any)  None
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LAB/BRANCH Laboratory of Neurobiology, Neuroscience Branch
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SECTION
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
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TOTAL MAN-YEARS: 1.00	PROFESSIONAL: 0.80	OTHER: 0.20
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CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input checked="" type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
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Phencyclidine (PCP) is a widely used drug of abuse which induces both excitation and euphoria in humans. The behavioral and psychotomimetic effects of PCP were originally thought to be mediated by sigma receptors, a receptor category originally postulated to account for the psychotomimetic actions of certain benzomorphans, including the prototypic agonist, N-allylnormetazocine. Data from recent radioligand binding experiments have demonstrated that PCP labels with high affinity an additional site (termed the PCP receptor) with a pharmacology distinct from that of the sigma receptor. In addition to their psychotomimetic effects in the central nervous system, PCP and N-allylnormetazocine have been reported to alter neuroendocrine function. Specifically, both compounds have been reported to stimulate hypothalamic-pituitary-adrenocortical secretion and to suppress prolactin and luteinizing hormone secretion in rats.



**Role of Sigma and Phencyclidine (PCP) Receptors in Endocrine Organs (Cont'd)**

Since PCP and N-allylnormetazocine bind with high affinity to both PCP and sigma receptors, the identity of the receptor(s) mediating the endocrine effects of these compounds is unknown. Furthermore, it is unclear whether the effects of PCP and N-allylnormetazocine are mediated in brain, or through direct actions at the pituitary or target endocrine organs. The aim of this study is to identify, characterize and localize sigma and PCP receptors in a variety of rat endocrine organs including the pituitary gland, adrenal, testis and ovary. Preliminary studies demonstrate the absence of high-affinity PCP receptors in endocrine tissue and the presence of high concentrations of sigma receptors with kinetic and pharmacological characteristics similar to those previously reported in the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER  Z01 DA00309-01 NBL
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Interleukin-1 in the Brain-Endocrine-Immune Axis		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E.B. DeSouza	Chief NBL, ARC, NIDA
Others:	D.E. Tracey	Visiting Scientist NBL, ARC, NIDA
COOPERATING UNITS (if any)  The Upjohn Company, Kalamazoo, MI		
LAB/BRANCH Laboratory of Neurobiology, Neuroscience Branch		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.20	1.20	0.00
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>             The cytokine, interleukin-1 (IL-1), is one of the key mediators of the immune response to stress, infection or antigenic challenge. In addition, IL-1 has a variety of effects in brain including its ability to cause fever and to induce slow-wave sleep. More recently, IL-1 has been reported to stimulate the hypothalamic-pituitary-adrenocortical axis. Whether IL-1 induces pituitary-adrenocortical secretion by direct stimulation of cells in the pituitary or indirectly through hypothalamic stimulation of corticotropin-releasing factor is controversial. Thus, the purpose of this study is to examine the role of IL-1 and its receptors in modulating the brain-endocrine-immune responses to stress. The initial studies will involve the identification, characterization and localization of IL-1 receptors in the central nervous system, pituitary and immune tissues including spleen and immune cell lines. Preliminary studies have identified IL-1 receptors in rat and mouse pituitary and in brain with characteristics similar to previously identified IL-1 receptors in EL-4 immune cells. In localization studies, IL-1 receptors in the pituitary appear to be situated primarily in the anterior lobe. Current studies are aimed at studying the interactions between IL-1 and other factors including corticotropin-releasing factor and monoamines in regulating adrenocorticotrophic hormone secretion from pituitary cells.           </p>		





## **Psychopathology and Cognitive Studies Branch**

**Jerome H. Jaffe, M.D., Acting Chief**

### **Introduction**

The Psychopathology and Cognitive Studies Branch previously consisted of two laboratories: Cognition/Human Performance and the Psychology of Vulnerability. With the merger of the Psychology of Vulnerability and Biology of Vulnerability within the Clinical Biology Branch, the Cognition/Human Performance Laboratory is the only Laboratory within the Psychopathology and Cognitive Studies Branch at the present time.

This Laboratory was established in recognition of the increased emphasis society is placing upon the cognitive and performance impairments produced by the use of psychoactive drugs, and in response to the ARC's responsibility under arrangements with the Department of the Army to study the effects of cholinergic blocking agents on human cognition and performance. Another major mission of the Laboratory is to apply newer computerized electrophysiological techniques to the assessment of individual differences associated with risk factors for drug abuse and with altered psychological and physiological functioning during drug withdrawal syndromes. Dr. Ronald Herning, a Visiting Scientist, has been functioning as its principal scientist.

**Cognition and Human Performance Laboratory -- Ronald Herning, Ph.D., Acting Chief**

### **Overview**

The Cognition and Human Performance Laboratory uses psychophysiologic, neurophysiologic and cognitive approaches to identify biological markers in populations at risk for drug abuse, cognitive and performance deficits produced by drugs of abuse, and deficits occurring during withdrawal which may prevent, or interfere with effective behavioral performance or drug cessation treatment. Specific research projects include studies to assess the effects of drugs of abuse on sensory and cognitive information processing, memory, attention, habituation, behavioral performance, and motor performance. In addition, an attempt is made to relate these findings to: (1) drug altered performance in the work place, (2) effective intervention and prevention strategies, (3) possible psychophysiologic and cognitive markers identified in populations at risk for drug abuse, and (4) neurophysiological mechanisms of cognitive drug reinforcement.

The Cognition and Human Performance Laboratory collaborates with the Biology and Psychology of Vulnerability Laboratory as well as the Biology of Dependence and Neuropharmacology Laboratories. New studies include (1) investigations of the electrophysiologic effects of cocaine and evaluation of drugs which might block the central nervous system (CNS) effects of cocaine, (2) examination of the relationship between the electrophysiologic and/or the cerebral metabolic (as measured by positron emission tomography [PET]) and subjective effects of cocaine and morphine, and (3) investigations of the effects of cholinergic agents on the behavioral and neurophysiologic indices of cognitive information processing. The Laboratory is also engaged in two collaborative studies with the Treatment and Early Intervention Branch. The first study monitors neurophysiologic and cognitive processing in persons withdrawing from cocaine. In the second study, the neurophysiologic and cognitive effects of buprenorphine maintenance and buprenorphine withdrawal are being monitored in opiate addicts.

Topographic mapping of multichannel electroencephalographic (EEG) and evoked potential data has enhanced the Laboratory's data analysis capacity. These color maps of electrical activity from the head during resting and cognitive processing can aid in the localization of drug effects in the human brain. The new technical advances may also facilitate the quantification of drug-produced alterations in cognition and performance, the characterization of cognitive and performance deficits observed during drug withdrawal, the evaluation of sensory and cognitive information processing abilities in populations at risk for drug abuse, and the investigation of drug effects on brain electrical activity as both a correlate of, and as a probe by which to delineate, drug-related activity.

## Summary of Ongoing Research

### Cocaine Studies

Over the past year, three studies investigated the effects of cocaine or cocaine withdrawal on human neurophysiology and cognition. Earlier studies conducted at ARC had found that cocaine increased EEG beta activity, blood pressure, pulse and subjective feelings, i.e., the "rush". However, the temporal sequence of the onset and offset of these measures had not been investigated, although this could provide valuable information about the mechanisms by which cocaine produces its euphorigenic effects. In analogous fashion, using pretreatment with an appropriate blocking drug might either block all of cocaine's effects, or selectively alter the time course and magnitude of only some of these effects. In both cases, the craving for the drug might be reduced and its mechanism of action clarified.

Following this strategy, single doses and 24-hour treatment with nifedipine, a calcium channel blocker, were employed in an attempt to antagonize the effects of cocaine. The results of this study could have both theoretical and practical importance. In this regard, the data indicate that the EEG



beta increase, which is observed with cocaine, was not clearly blocked by a single dose of nifedipine. In contrast, 24-hour treatment with nifedipine blocked the cocaine-induced increase in beta activity in one subject. However, the side effects of this treatment precluded further testing.

In a different line of experimental inquiry, the effects of cocaine on the multichannel EEG recording are compared with regional cerebral glucose utilization measured using PET in humans. Both techniques can provide critical information regarding the localization of the effects of cocaine on the brain. Collaborators of the Laboratory are performing the PET scans which can only provide data on regional cerebral glucose utilization for a time interval that is at least 10-15 minutes in duration. The EEG measures supplement the PET data by providing information about cortical electrical events at intervals as short as one second. Thus, if a cortical area is involved in the state of euphoria produced by cocaine, or if it is reflected in the activity of subcortical structures, the EEG data can provide critical information about the time course of any activity observed as well as some suggestions about the brain areas involved in the cocaine-related activity.

To date, six subjects have been tested in this protocol. The subjects exhibited a dose-dependent increase in EEG beta activity in the frontal, parietal and temporal areas of the cortex following administration of 40 mg of intravenously administered cocaine as compared to an intravenously administered placebo. The increase in beta activity lasted 20 minutes or more and paralleled more closely feelings of euphoria than the state described as a rush.

A third study ongoing in the Laboratory monitors aspects of cognition and behavioral performance in heavy intravenous cocaine users withdrawing from cocaine. Information processing deficits were observed in heavy cocaine users in withdrawal in earlier studies. Such deficits seem likely to interfere with effective treatment and, perhaps, contribute to relapse. In cocaine users not seeking treatment, periods without cocaine may produce impaired job performance. Thus, the current study was designed to carefully document cognitive processing alterations during cocaine withdrawal with a combination of sensitive behavioral tasks and cognitive event related potential measures. The behavioral tasks measure attention, stimuli evaluation, memory, and vigilance, and are responsive to task-relevant rare events and visual motor tracking. Sleep and awake periods are monitored by a wrist activity meter.

So far, thirteen heavy intravenous cocaine and 6 control subjects have been tested. While testing is still ongoing, a clear pattern is emerging. Cognitive performance deficits are observed over a 3-week period following the cessation of cocaine use. Notably, the maximal impairment is observed during the first three days of abstinence.



## **Opioid Studies**

Studies on the effects of morphine on scalp EEG activity and regional cerebral glucose utilization have been continued. Data from the EEG recordings and the PET scans are being compared to further trace the location of morphine effects in the brain. In the twelve subjects evaluated to date, a dose-dependent increase in EEG delta and theta power was observed. The increase was found to occur approximately 15 minutes after an intramuscular injection and to continue for the next 30 minutes. Frontal and temporal areas of the cortex are involved in this EEG effect.

The effects of buprenorphine maintenance and subsequent withdrawal were investigated in 16 heroin users. Various aspects of cognition were measured using a battery of cognitive tasks throughout the maintenance and withdrawal phases. In some of the tasks, neurophysiologic measures of cognitive information processing supplemented the behavioral measures of cognitive performance. Pupil size and the pupillary light reflex were also measured. Seven subjects have completed the protocol.

The specific aim of the cognitive testing is to determine whether there are severe cognitive deficits when addicts are dosed every other day with buprenorphine. The testing during withdrawal is designed to determine the extent and time course of cognitive disruption during buprenorphine withdrawal.

## **Cholinergic Studies**

An additional study for the military during the current year examined physostigmine's effects on basic sensory electrophysiology and cognitive information processing. A 1.0 mg intravenous dose of physostigmine was compared to placebo, with and without pretreatment with methscopolamine (5 mg orally). The tasks included eyes-open EEG, physiological tremor, pattern reversal visual-evoked response, self-paced motor potential, rare event monitoring and the Sternberg memory test. Ten subjects have been tested. Preliminary data suggest that stimulus evaluation is altered by this dose of physostigmine, and that this alteration is not blocked by methscopolamine. Data from other tasks require further analysis.

## **Vulnerability Studies**

Many factors appear to be important in the etiology of drug abuse. Both antisocial behavior and early aggression are risk factors for later drug use. During the preceding year, information processing was studied in two groups of non-institutionalized adolescents with two levels of delinquency. The more delinquent group (N=12) was selected because of school-related conduct problems. The less delinquent group (N=13) consisted of age-, IQ-, race- and neighborhood-matched groups of adolescents. Spontaneous EEG and event related potentials were recorded from the scalp and extensive psychometric data were obtained. Both sensory and cognitive information processing deficits were observed in the more delinquent group. Moreover, the latency

of Wave V of the auditory brainstem evoked response was delayed. Further, N100 latency was decreased and the frontal slow wave was absent in the more delinquent individuals. Further data analysis indicated that P300, a measure of stimulus evaluation, was reduced in all adolescents who used illicit drugs, regardless of their history of aggression.

In another ongoing project, the Laboratory collaborates with several other laboratories in measuring biological markers of impulsivity and/or aggression. Volunteers with varied drug abuse histories are assessed using a number of psychiatric and personality batteries. They are subsequently challenged with pharmacological probes and an oral glucose load while neuroendocrine subjective and electrophysiological measures are made. Thus far, 46 subjects have completed the study.

### **Nicotine Studies**

During the current year the Laboratory's efforts were also directed toward the analysis of a major study investigating tobacco withdrawal in heavy smokers. EEG, cognitive and performance measures were used to examine cognitive processing during a 10-day period of tobacco withdrawal in heavy smokers. Subject testing ended in the previous fiscal year. A neurophysiologic index of selective attention was impaired during tobacco withdrawal and the impairment persisted over the entire 10-day deprivation period. Stimulus evaluation time as measured by P300 latency, the depth of stimulus evaluation as measured by P300 amplitude, and simpler tasks on the computerized cognitive battery were found to be affected only early during the tobacco deprivation period.

Cognitive deficits are apparent during nicotine abstinence and they may contribute to relapse during treatment. During nicotine withdrawal, the deficits have two different time courses: one which dissipates after 5 to 7 days and one which persists at least 10 days. The first appears to affect stimuli evaluation and the second affects selective attention. The efficacy of nicotine gum in relieving these cognitive deficits was also investigated, although these results are not yet fully analyzed.

## Publications and Abstracts

Herning, R.I., Glover, B.J., Sano, M., Cascella, J., Reddish, R., London, E.D., and Jaffe, J.H.: The cortical and temporal mapping of EEG changes produced by intravenous cocaine. Psychopharmacology 25: 454, 1988.

Fishbein, D.H., Herning, R.I., Pickworth, W.B., Haertzen, C.A., Hickey, J.E. and Jaffe, J.H.: Brainstem evoked response potentials in adult male drug abusers with self-reported histories of aggressive behavior. Biol. Psychiat., In press.

Herning, R.I., Hickey, J.E., Pickworth, W.B. and Jaffe, J.H.: Auditory event related potential in adolescents at risk for drug abuse. Psychiatry, In press.

Snyder, F.R. and Henningfield, J.E.: Effects of nicotine administration following 12 hours of tobacco deprivation. Psychopharmacology 97: 17-22, 1989.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA02001-03 CHP
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Mapping the Effects of Opioid Agonists by Positron Emission Tomography and EEG
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: R.I. Herning	Acting Chief	CHP, ARC, NIDA
Others: F.R. Snyder	Scientist	CHP, ARC, NIDA

COOPERATING UNITS (if any)  Neuropharmacology Laboratory, Johns Hopkins Hospital
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LAB/BRANCH
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SECTION Cognitive Studies and Human Performance Laboratory
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
--

TOTAL MAN-YEARS: 0.50	PROFESSIONAL: 0.50	OTHER:
--------------------------	-----------------------	--------

CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Effects of morphine on the scalp EEG and fluorodeoxyglucose (FDG) positron emission tomography (PET) scans are being compared to determine the brain areas invoked in euphoria. The Cognitive Studies and Human Performance Laboratory is collecting and analyzing the EEG data from 20 scalp locations from post-addicts receiving a placebo, or 15 and 30 mg injections of morphine. In addition, these subjects subsequently received FDG PET scans while receiving a placebo and 30 mg of morphine. The PET scans are performed by the Laboratory's collaborators. The EEG data provide insight into the time course of the electrophysiologic effects of a mu agonist in humans, as well as the cortical distribution of mu effects, while the PET techniques do not by themselves provide information about the time course of these effects. Twelve subjects had increased EEG delta and the theta power beginning 15 minutes, and persisting 45 minutes after the intramuscular injection. These EEG changes were dose dependent. The relationship between these EEG changes and subjective effects of morphine is being investigated.
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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA02101-04 CHP
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Acute Abstinence From Tobacco: Electrophysiological and Cognitive Signs

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	W.B. Pickworth	Scientist	CHP, ARC, NIDA
	R.I. Herning	Acting Chief	CHP, ARC, NIDA
	F.R. Snyder	Scientist	CHP, ARC, NIDA

COOPERATING UNITS (if any)

Biology of Dependence Laboratory (J.E. Henningfield and R.D. Nemeth-Caslett)

LAB/BRANCH  
Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.10	PROFESSIONAL: 0.10	OTHER:
--------------------------	-----------------------	--------

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Laboratory's efforts were directed toward the quantification of the cognitive and performance deficits during nicotine withdrawal and the treatment of these deficits with nicotine chewing gum. EEG, and cognitive processes were monitored during a ten-day period of tobacco withdrawal in heavy smokers. Some of the changes persisted over the entire ten day deprivation period. These measures included EEG alpha frequency, theta power, performance on selected cognitive tasks (especially a rapid arithmetic task) and a cognitive event related potential measure (N100 amplitude). Stimulus evaluation time, as measured by P300 latency, and the depth of the stimulus evaluation battery were affected early during the tobacco deprivation period, but returned to smoking levels later during the deprivation period. Thus, the cognitive deficits are apparent during the abstinence from tobacco and may contribute to relapse during treatment. The deficits during withdrawal have at least two different components, one affecting stimulus evaluation which dissipates after 5 to 7 days of abstinence, and one affecting attention which is accompanied by lower arousal and which persists ten days or longer. During this year, these data were analyzed and two papers submitted for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA03101-03 CHP
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Effects of Atropine on Cognitive Information Processing		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.E. Henningfield      Chief	BPD, ARC, NIDA
Others:	W.B. Pickworth      Scientist	CHP, ARC, NIDA
	R.I. Herning      Acting Chief	CHP, ARC, NIDA
	F.R. Snyder      Scientist	CHP, ARC, NIDA
COOPERATING UNITS (if any) Biology of Dependence Laboratory		
LAB/BRANCH Cognitive Studies and Human Performance Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.10	PROFESSIONAL: 0.10	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>An extensive battery of sensory and cognitive electrophysiological tasks is used to assess sensory, cognitive and performance deficits produced by atropine. The tasks include eyes-open and eyes-closed EEG, brainstem auditory- evoked response, pattern reversal visual-evoked response, the auditory rare-event monitoring task, the auditory continuous performance task and the Sternberg auditory memory task (both immediate and delayed). Each of four doses of atropine (0, 2, 4 and 6 mg/70 kg) is investigated on two occasions. Eight subjects have been tested on these procedures.</p> <p>The purpose of the study is to better understand the effects of cholinergic agents on cognition and performance, in particular, the site at which the information processing sequence effects of atropine are exerted. The EEG and evoked response data have been reported in military and scientific journals. Atropine, at doses of 4 mg or greater, increases EEG slowing and reduces cognitive evoked potentials and performance.</p>		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA03111-03 CHP
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Effects of Benzodiazepines on Cognitive Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.I. Herning	Acting Chief	CHP, ARC, NIDA
Others:	W.B. Pickworth	Scientist	CHP, ARC, NIDA
	F.R. Snyder	Scientist	CHP, ARC, NIDA

COOPERATING UNITS (if any)  
Biology of Dependence Laboratory

LAB/BRANCH  
Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.10	PROFESSIONAL: 0.10	OTHER:
--------------------------	-----------------------	--------

CHECK APPROPRIATE BOX(ES)  
☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

An extensive battery of sensory and cognitive electrophysiological tasks was used to assess sensory, cognitive and performance deficits produced by diazepam. The tasks include eyes-open and eyes-closed EEG, brainstem auditory-evoked response, pattern reversal visual-evoked response, the auditory rare-event monitoring task, the auditory continuous performance task and the Sternberg memory task (both immediate and delayed). Six doses (0, 2.5, 5.0, 10.0, 20.0 and 40.0 mg) of diazepam were used. Nine subjects were tested.

The purpose of the study was to determine the site at which the information processing sequence effects of benzodiazepines are exerted. Memory deficits have been previously noted, but it is yet unclear whether the deficits are due to poor encoding of the information or loss of the newly formed memory trace. It is hoped that the study will be important in understanding the ways in which drugs of this class impair functioning.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA03301-01 CHP
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Electrophysiological Measures of Conduct Disorder (Aggression) in Adolescents</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: J.H. Jaffe	Director	ARC, NIDA
Others: R.I. Herning W.B. Pickworth	Acting Chief Scientist	CHP, ARC, NIDA CHP, ARC, NIDA
COOPERATING UNITS (if any)  Early Intervention Laboratory (B.S. Brown and J.E. Hickey)		
LAB/BRANCH Cognition and Human Performance Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.10	PROFESSIONAL: 0.10	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input checked="" type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Adolescents with a history of violence are likely to be at risk for drug abuse. This project investigates a group of antisocial adolescents and a group of age-, IQ-, race-, and neighborhood-matched adolescents who participated in a study which included psychometric and electrophysiological testing. The Cognitive Studies and Human Performance Laboratory is primarily concerned with the electrophysiological measures. The more aggressive group differed from the control group on many electrophysiological measures. Wave V of the brainstem auditory-evoked response was significantly longer in the more aggressive adolescents. The latency of the N100 of a tone-evoked brain potential was shorter in the more aggressive group than the control group. Further, the slow wave did not show the usual anterior to posterior distribution in a more aggressive group. P300 amplitude to the target tone in a cognitive task was lower in the adolescents who used illicit drugs than those who did not, regardless of the history of aggression. EEG alpha activity was reduced and theta power was increased in the violent group. The constellation of sensory and cognitive differences suggests that adolescents displaying violent antisocial behavior may have a major information processing disorder, which, in some respects, is similar to attention deficit disorder and yet differs in other respects. Moreover, drugs may be used by these antisocial individuals to normalize cognitive processing.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA05801-02 CHP
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Mapping the Effects of Cocaine by Positron Emission Tomography</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	R.I. Herning	Acting Chief  CHP, ARC, NIDA
Others:	F.R. Snyder	Scientist  CHP, ARC, NIDA
COOPERATING UNITS (if any)  Neuropharmacology Laboratory (E.D. London), Johns Hopkins Hospital (D.F. Wong)		
LAB/BRANCH Cognitive Studies and Human Performance Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.40	PROFESSIONAL: 0.40	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>The effects of cocaine on scalp EEG and fluorodeoxyglucose (FDG) positron emission tomography (PET) scans are being compared to determine the brain areas involved in the cocaine-induced euphoria. In previous studies, cocaine was found to increase EEG beta power. However, the distribution of cortical areas responsible for the EEG beta increases and the time course of this increase have not as yet been determined. The present study was designed to address these two questions. It is hoped that the complimentary nature of the EEG and PET data may delineate the anatomical and electrophysiologic mechanisms involved in cocaine-induced euphoria.</p> <p>Six subjects administered either placebo, 20 mg or 40 mg of cocaine in double-blind order were tested using EEG measures. It was found that EEG beta increased in dose-dependent manner starting immediately after the injection and continuing for twenty minutes. The increased EEG beta power was maximal in frontal, temporal and partial cortical areas. The relationship between the increase in beta power and subjective state is currently being investigated.</p>		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA05901-02 CHP

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cholinergic Pharmacology: Cognitive and Neurophysiologic Screen

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R.I. Herning Acting Chief CHP, ARC, NIDA

COOPERATING UNITS (if any)

Biology of Dependence Laboratory

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

0.30

PROFESSIONAL:

0.30

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A battery of tasks is being used to assess sensory, cognitive, and motor deficits produced by physostigmine. The tasks (eyes-open EEG, physiological tremor, pattern reversal visual-evoked response, self-paced motor potentials, rare event monitoring, and Sternburg tasks) were designed to test neurophysiological indices of brain processing as well as behavioral performance. Sensory and cognitive performance were tested both after placebo or methscopolamine pretreatment. The pretreatment with methscopolamine tests whether the performance deficit was due to the peripheral effect of physostigmine.

The purpose of the study is to better understand the effects of cholinergic agents on sensory, motor and cognitive performance at the neurophysiological level. Cholinesterase inhibitors are commonly used biological warfare agents. Thus, techniques for determining the cognitive impairments produced by anticholinergics and safe models for inducing cholinergic stimulation may be important steps in developing useful and effective antidotes to cholinesterase inhibitors. Ten subjects were tested and the data are being analyzed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA06201-02 CHP
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Buprenorphine Maintenance and Withdrawal on Cognitive/Neurophysiologic Measures

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.I. Herning	Acting Chief	CHP, ARC, NIDA
Others:	W.B. Pickworth	Scientist	CHP, ARC, NIDA
	F.R. Snyder	Scientist	CHP, ARC, NIDA

COOPERATING UNITS (if any)  
Research Support Branch (R.E. Johnson and P.J. Fudala), Early Intervention Branch (B.S. Brown and W.W. Weddington)

LAB/BRANCH  
Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 0.80	PROFESSIONAL: 0.80	OTHER:
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CHECK APPROPRIATE BOX(ES)

<input checked="" type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Buprenorphine is being evaluated for detoxification and maintenance in the treatment of heroin addiction. As part of an extensive series of tests, the effects of buprenorphine maintenance and subsequent withdrawal are being investigated in heroin users in an effort to determine whether there are severe cognitive deficits when addicts are dosed every other day with buprenorphine. After being maintained on buprenorphine daily or every other day by sublingual dosing, the addicts are abruptly withdrawn. Various aspects of cognition are measured using a battery of cognitive tasks throughout the maintenance and withdrawal phases. In some of these tasks, neurophysiologic measures of cognitive information processing supplemented the behavioral measures of cognitive performance. Pupil size and the pupillary light reflex are also measured. The effects of the two dose conditions on cognitive processing are to be compared. However, the effects of abrupt buprenorphine withdrawal on cognition are to be evaluated. Pupil measures were included because of their sensitivity to opiate effects. Sixteen subjects have completed the protocol. No differences were found on EEG measures for daily and every other day dosing. The cognitive data are currently being analyzed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA06801-02 CHP
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cognitive and Neurophysiologic Signs of Cocaine Withdrawal		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	R.I. Herning	Acting Chief CHP, ARC, NIDA
Others:	F.R. Snyder	Scientist CHP, ARC, NIDA
COOPERATING UNITS (if any)  Early Intervention Branch (B.S. Brown & W.W. Weddington)		
LAB/BRANCH Cognitive Studies and Human Performance Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.60	PROFESSIONAL: 0.60	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Cognitive impairments and sleep disruption have been reported in patients withdrawing from cocaine. However, the nature of these disorders has yet to be documented in clinical laboratory studies. The present study evaluates cognitive information processing in subjects on a clinical ward who are withdrawing from cocaine using a battery of tasks (auditory rare-event monitoring, complex visual rare-event monitoring, Sternburg memory, and visual motor tracing). Sleep quality and duration are monitored by a subjective questionnaire. Twenty subjects, including controls, have been tested in this study over a one-month withdrawal period.  It is hoped that clarification of the nature of the cognitive deficits and of sleep loss which occur will lead to more effective treatment strategies for cocaine withdrawal.		





## **Treatment and Early Intervention Research Branch**

**Barry S. Brown, Ph.D., Chief**

### **Overview**

The Treatment and Early Intervention Research Branch was organized in September 1986 to study the efficacy of treatment and early intervention strategies. The Branch conducts research regarding the efficacy of new psychopharmacologic and behavioral treatments for drug dependence, especially for cocaine and intravenous (IV) heroin use. In addition, the Branch explores the efficacy of strategies to prevent or reduce drug-taking behavior among young people with a high vulnerability for drug use and/or abuse. Research is carried out on both the ARC Inpatient Unit and its recently completed Outpatient Unit. In addition, the Branch makes use of treatment facilities located in the Baltimore area. The Treatment and Early Intervention Research Branch is divided into two laboratories.

#### **1. Clinical Trials Laboratory - Barry S. Brown, Ph.D., Chief**

The Clinical Trials Laboratory is responsible for the conduct of studies assessing the efficacy of innovative treatment approaches. The interventions studied are primarily psychopharmacological and/or behavioral in nature and evaluations of the various modalities are conducted in both inpatient and outpatient settings. Studies explore the efficacy of interventions with a view toward the replication of effective strategies by the service delivery community. Additional studies examine issues significant to the service delivery process.

These objectives are being pursued using a variety of research techniques, including: (1) the use of single-blind and double-blind procedures to evaluate various pharmacologic interventions, (2) the use of experimental designs employing random assignment of subjects and/or comparison groups to evaluate the impact of psychosocial/behavioral interventions, (3) obtaining and quantifying observational data to clarify behaviors significant to the conduct of drug abuse treatment.

Studies are frequently conducted in collaboration with other laboratories of the ARC and with cooperating facilities of the State of Maryland Drug Abuse Administration. Within the ARC, joint projects are being conducted in association with the Cognitive Studies and Human Performance Laboratory, the Biology and Psychology of Vulnerability Laboratory, and the Chemistry and Drug Metabolism Laboratory. In addition, several programs of the Maryland Substance Abuse Authority have indicated a willingness to join with the Branch as appropriate. Currently, the Man Alive Methadone Maintenance Program is working with the Branch in a study examining the use of psychopharmacologic strategies with methadone maintenance clients.

Long-term goals of the Clinical Trials Laboratory will continue to be to explore and clarify issues significant to the treatment process and to examine interventions which have promise for service delivery. For the foreseeable future, concerns about the impact of AIDS on drug abuse treatment, issues related to concurrent psychiatric diagnoses, and the need to provide effective treatment for cocaine abusers will likely remain dominant.

## **I. Summary of Ongoing Research**

### **A. Effects of Pharmacologic Agents on Cocaine Abuse Treatment: Weddington, W.W., Brown, B.S. and Jaffe, J.H.**

Systematic investigation comparing different pharmacologic regimens for cocaine dependence with each other under blind conditions are only beginning to be reported in the literature. This study involves the comparison of desipramine hydrochloride and amantadine hydrochloride in regimens which earlier open-trial investigations had suggested might be useful in treatment of cocaine abuse. A third test group receives placebo drug. The treatment regimen for the three randomly assigned groups lasts a 12-week period and involves twice weekly counseling in addition to daily medication.

The measures in this study assess cocaine craving, sleep satisfaction, mood, drug use, psychological symptoms, and depression on a weekly or more frequent basis. Reports of side effects, as well as blood pressure and pulse readings are obtained routinely. In addition, blood samples are drawn periodically to assess compliance with the therapeutic regimen. Followup is being performed to assess the functioning of clients six and twelve months after the completion of treatment.

The study permits an assessment of two of the major pharmacologic strategies that have been suggested for use in outpatient treatment of cocaine abusers. Thorough initial psychological assessments permit subsequent analysis of factors that predict a high probability of dropout or failure to improve. Given the increase in cocaine dependence and the public concern about that drug, there is particular urgency for a study designed to clarify treatment modalities which may be useful in alleviating this problem.

### **B. Use of Pharmacologic Agents for Cocaine Dependence in Methadone Maintenance Clients: Kolar, A., Brown, B.S. and Jaffe, J.H.**

Cocaine use has long been associated with opiate dependence. Indeed, the two drugs have been used together to achieve particular psychic states. Increasingly, there have been reports from methadone programs of significant levels of cocaine use by persons stabilized on methadone. Under double-blind conditions, this study



explores the efficacy of amantadine hydrochloride and desipramine hydrochloride as compared with a placebo condition to determine the utility of the different pharmacologic regimens in cocaine-dependent methadone-maintained clients. In this study, cocaine-dependent methadone maintenance clients in an area treatment program are randomly assigned to each of the three treatment groups described. They receive both methadone and the study medication on a daily basis. Counseling and other clinic activities are available to all client groups.

The measures employed involve weekly or more frequent assessments of cocaine craving, sleep satisfaction, mood, psychological symptoms, depression and drug use. Reports of side effects, as well as blood pressure and pulse readings, are obtained routinely. In addition, blood samples are obtained on a weekly basis for toxicological analyses, both for purposes of safety and to monitor treatment compliance. Counselors report depression and overall psychological functioning on a once weekly basis; in addition, assessment will be made of functioning at 6- and 12-month intervals after treatment.

Clarification of the role which may be played by available pharmacologic agents in retaining clients in methadone treatment can be significant not only to the process of drug abuse rehabilitation, but also to the containment of acquired immune deficiency syndrome (AIDS) and human immunodeficiency virus (HIV) as well.

**C. Behavioral and Physiological Effects Associated with Acute Cessation of Cocaine: Weddington, W.W., Cone, E.J., Dax, E.M. and Herning, R.I.**

Cocaine cessation has been reported as leading to significant depressive symptoms with concomitant irritability, anxiety and sleep abnormality. These observations have been largely restricted to outpatient populations. Thus, the goal of the current investigation is to clarify behavioral and physiological functioning associated with the cessation of cocaine use under controlled, i.e. inpatient, conditions.

Individuals meeting criteria for cocaine dependence are admitted to a study lasting up to six weeks. Measures are made at prescribed intervals to assess cognitive performance, neuroendocrine functioning, the excretion of cocaine and its metabolites, psychological status, depressive ideation, drug craving, sleep satisfaction/dissatisfaction, and cardiovascular functioning. A particular aim of this study will be to clarify both the extent of sleep disorder associated with cessation of cocaine use and the relationship of that disorder to other measures of psychobiologic functioning. Subjects will be available for followup assessments every other month up to one year post-discharge.

**D. Characteristics of Waiting List Clients and Behaviors: Brown, B.S., Hickey, J.E. and Jaffe, J.H.**

In much of the country, treatment programs report that they are maintaining lengthy waiting lists that delay, if not frustrate, entrance into drug abuse treatment. To date, no studies had been conducted that are designed to examine the behaviors of waiting list applicants with regard to prosocial/antisocial functioning, as well as efforts to locate alternative treatment opportunities, and/or intentions to remain available to the treatment program initially contacted. The attitudes and behaviors of persons on a waiting list can have definite impact on these individuals' subsequent program compliance and their functioning in the community. Indeed, these concerns have been newly aroused by the threat of HIV infection posed by intravenous drug use.

This project involves drawing a random sample of individuals who had placed themselves on the waiting list for an area residential drug abuse treatment program. The sample was stratified by gender and length of time on the waiting list. The measures in use are designed: (1) to clarify the demographics, background and psychological functioning of waiting list clients; (2) to examine functioning in the community in regard to drug use, employment and antisocial activities; (3) to assess efforts to obtain drug abuse treatment; and (4) to evaluate risk-taking/risk-reduction behaviors relative to HIV infection. In addition, the study seeks to explore issues in terms of community pressures for and against entry into treatment.

Study of the behaviors of individuals who are awaiting entry into treatment can help clarify questions which have arisen about whether individuals remain accessible to treatment programs, as well as about the cost, if any, to society which may be associated with maintaining waiting lists. In addition, this type of study could lay the groundwork for the development of strategies designed to encourage clients to remain available to treatment programs. Moreover, this study may clarify the extent to which IV cocaine users are practicing risk reduction behaviors in relationship to HIV infection and identify approaches which IV cocaine users have made in an effort to modify risk-taking behaviors related to the threat of AIDS.

**E. Opioid Dependence: Pharmacological Study of Buprenorphine: Johnson, R.E., Fudala, P.J., Dax, E., Cone, E., Herning, R.I., et al.**

Buprenorphine is a partial agonist of the morphine type with an analgesic potency 25-50 times that of morphine. Buprenorphine produces: subjective effects acceptable to opioid abusers; a duration of physiological and subjective effects similar to

methadone; and blockade of exogenously administered opiates. Studies assessing buprenorphine's effects on opioid self-administration and its use in detoxifying opioid addicts have been positive.

The use of illicit drugs intravenously has been correlated with the AIDS epidemic. In order to decrease illicit IV drug use, additional interventions for opioid addicts are needed. It has been shown that many opioid addicts refuse to seek treatment due to the limited chemotherapeutic interventions available. Given this, the development of alternative therapeutic interventions seems most appropriate and necessary.

This study is designed to assess the pharmacodynamic and pharmacokinetic properties of buprenorphine in controlled inpatient and outpatient trials. This study will assess: (1) a rapid dose induction procedure; (2) the clinical efficacy of different dose regimens; (3) the duration of effective blockade; and (4) withdrawal from different dose regimens. For each dosage regimen, twelve subjects will be studied using a battery of subjective, physiological, cognitive, pharmacokinetic, neurohormonal and electrophysiological measures.

It is hoped that data collected through this study will add to the basic clinical knowledge presently available about using buprenorphine in an opioid-dependent population.

**F. Assessment of Methadone Maintenance Treatment: Ball, J.C. and Brown, B.S.**

The use of methadone maintenance has continued both as a controversial and widely employed treatment form. The controversy stems from concerns about the efficacy of methadone maintenance treatment and the level and types of services provided in methadone programs. This study was initiated to investigate the efficacy of program and treatment variables associated with successful client outcome in seven methadone maintenance programs in Baltimore, New York and Philadelphia.

The subject population included 633 male methadone-maintained patients located at the several programs studied. Face-to-face interviews were conducted with all subjects on two occasions. In addition, data were gathered about the program services offered clients and the characteristics of the treatment environment. Analyses will be conducted to examine the extent to which successful outcome, i.e. diminution of drug-taking behavior, is demonstrated at these facilities, and the client and program variables which may be associated with successful outcome.



Clarification of the efficacy of methadone maintenance treatment in reducing IV drug use and thereby halting the spread of HIV infection, as well as in increasing current understanding of the role played by differing treatment and program variables, will be essential in improving drug abuse treatment programs and services.

**G. Efficacy of Fluoxetine in the Treatment of Cocaine and PCP Dependence: Covi, L., Brown, B.S. and Jaffe, J.H.**

Efforts to contain cocaine dependence and the craving associated with it have focused on the use of pharmacologic adjuncts with a primary impact on the dopaminergic system. Data from the field of neurosciences also implicate the serotonergic system as being disrupted by cocaine and phencyclidine (PCP). In an effort to examine the possible efficacy of serotonergic blockers in limiting the craving and use of cocaine and PCP, fluoxetine was selected for study; it is an antidepressant with particular potential in this regard. Thus, a study was begun comparing the efficacy of fluoxetine with desipramine, bromocriptine, and a placebo drug (i.e., a low dose of diphenhydramine).

In view of the specific interest in fluoxetine, initial investigations focused on comparing fluoxetine and placebo. To date, a sample of 35 cocaine-dependent subjects has been placed on fluoxetine and 11 on placebo; 8 PCP subjects have been placed on fluoxetine and 5 PCP subjects on placebo. Subjects are randomly assigned to fluoxetine and placebo groups and maintained under double-blind conditions. An intake battery assessing drug use, craving, psychological functioning, sleep disturbance, and physical health is administered. Subsequently the subjects receive weekly assessments of drug use, craving, and selected aspects of psychological functioning. Subjects will also be seen at 3, 6, and 12 months post-treatment.

It is hoped that the results of this study will clarify the possible utility of this serotonergic reuptake blocker as a pharmacologic adjunct in the treatment of both cocaine and PCP dependence.

## Publications

Ball, J.C., Lange, W.R. and Brown, B.S.: The Prevalence of IV Drug Use and Needle-Sharing among Heroin Addicts during and after Methadone Maintenance Treatment. Proceedings of the 50th Annual Scientific Meeting, Committee on Problems of Drug Dependence, In press.

Ball, J.C. and Corty, E.: Basic Issues pertaining to the Effectiveness of Methadone Maintenance Treatment. Compulsory Treatment of Drug Abuse: Research and Clinical Practice. NIDA Research Monograph, 1988.

Ball, J.C. and Corty, E.: Policy Issues pertaining to the Treatment of Heroin Addicts in the United States - With Particular Reference to Methadone Maintenance Therapy. Proceedings of the Dutch-American Conference: The Effectiveness of Drug Abuse Treatment, In press.

Ball, J.C., Lange, W.R., Myers, C.P. and Friedman, S.: Reducing the risk of AIDS through methadone maintenance treatment. J. Health Soc. Behav., In press.

Brown, B.S.: Contributions of the DARP to Treatment Research Methods and Policy. In Applications of Interactionist Psychology. New York, NY, Earlbaum Press, 1988.

Brown, B.S.: Civil commitment - An international perspective. J. Drug Issues, In press.

Brown, B.S. and Beschner, G.M.: AIDS and HIV infection - Implications for drug abuse treatment. J. Drug Issues, In press.

Brown, B.S.: AIDS: Implications for drug abuse treatment. NIDA Notes, 1988.

Brown, B.S.: The American Addiction Treatment Scene: An Overview. Proceedings of the Dutch American Conference - The Effectiveness of Drug Abuse Treatment, In press.

Brown, B.S., Hickey, J.E., Chung, A.S., Craig, R.D. and Jaffe, J.H.: Waiting for Treatment: Behaviors of Cocaine Users on a Waiting List. Proceedings of the 50th Annual Scientific Annual Scientific Meeting, Committee on Problems of Drug Dependence, In press.

Brown, B.S.: The Growth of Drug Abuse Treatment Systems. Handbook of Drug Control in the United States, In press.

Brown, B.S.: Civil Commitment - International Issues. In Compulsory Treatment of Drug Abuse: Research and Clinical Practice, NIDA Research Monograph, 1988.

## Publications (Cont'd)

Corty, E., Ball, J.C. and Myers, C.P.: Psychological symptoms in methadone maintenance patients: Prevalence and change over treatment. J. Consult. Clin. Psychol. 56(6): 1-2, 1988.

Large, W.R., Ball, J.C., Pfeiffer, M.B., Snyder, F.R. and Cone, E.J.: The Lexington addicts, 1971-1972: Demographic characteristics, drug use patterns, and selected infectious disease experience. Int. J. Addict., In press.

Platt, J.J., Buhringer, G., Kaplan, C.D., Brown, B.S. and Taube, D.O.: The prospects and limitations of compulsory treatment for drug addiction: Results of a German-American workshop. J. Drug Issues, In press.

Weddington, W.W. and Brown, B.S.: Acceptance of HIV-antibody testing by persons seeking outpatient treatment for cocaine abuse. J. Subs. Abuse Treat. 5: 145-149, 1988.

Weddington, W.W. and Brown, B.S.: Acceptance of HIV testing. NIDA Notes, In press.

Weddington, W.W. and Brown, B.S.: HIV-antibody testing of patients seeking treatment for drug abuse. Institute on Hospital and Community Psychiatry, Accepted.

## 2. Early Intervention Laboratory -- Barry S. Brown, Acting Chief

### Overview

The Early Intervention Laboratory is responsible for the conduct of studies designed to clarify the efficacy of interventions especially targeted to adolescents and pre-adolescents who are at high risk for drug-taking behaviors. An objective of the studies undertaken is to clarify the utility of interventions for use with young persons whose drug-taking behaviors have resulted, or threaten to result, in family and community conflict. Focus is also placed on psychobiological issues of substance abuse and dependence, as well as on issues significant to the development of effective prevention programming.

The objectives being pursued make use of a variety of study procedures, including: (1) experimental research design involving random assignment to control and/or comparison groups for purposes of clarifying the efficacy of early interventions or preventive strategies; (2) use of structured interview schedules designed to clarify issues in the development of drug-taking behaviors; (3) the use of psychobiologic assessment to study the development of drug-taking behaviors and to clarify differences between vulnerable and less vulnerable populations. In the conduct of its research,



the Laboratory has allied itself with additional laboratories of the Addiction Research Center, most notably the Biology and Psychology of Vulnerability Laboratory and the Cognitive Studies and Human Performance Laboratory. In addition, the Laboratory is working with adolescent treatment programs associated with the Maryland Substance Abuse Administration and the Maryland Juvenile Services Administration.

The long-term goals of the Early Intervention Research Branch are to explore the efficacy of early intervention strategies designed to contain young persons' deepening involvement in substance abuse and to clarify etiologic issues in the development of substance abuse. A particular emphasis has been placed on clarifying the relationship between the development of drug using behaviors and those behaviors associated with aggressive conduct disorders. Issues of the extent to which learning disorder and early school failure contribute to the development of substance abusing and other antisocial behaviors also require further clarification.

#### **Summary of Ongoing Research**

##### **A. Family Intervention with Young Chronic Cocaine Abusers: Rose, M., Weddington, W.W., Brown, B.S. and Jaffe, J.H.**

There is increasing interest in the use of family therapy in treating drug abuse, in particular with youthful substance abusers. At the same time, technological advances have made it possible for parents and others to monitor and help contain drug-taking behaviors. With this as background, a study was initiated to examine the utility of traditional family therapy, in which the substance abuse is viewed as a symptom of family disruption, with a family therapy strategy that permits parents to monitor drug use by their adolescents in treatment (using the results of urine screening) and to make drug use the primary focus of family treatment. Given the particular significance of cocaine use among young people, the study focus has been placed on the treatment of youthful cocaine users.

Youthful cocaine users and one or more family members were randomly assigned to groups providing either traditional family therapy or family therapy/drug use monitoring. Treatment was designed to last a period of 24 weeks, with twice weekly sessions (1 family and 1 individual) for the entire period. Counselors followed a standard regimen of family therapy, differing only in the use of urine testing. Measures were obtained regarding substance abuse, psychological functioning, family functioning, impulse control and aggressivity, and school-based performance.

##### **B. Spread of Cocaine Use: Hickey, J.E. and Brown, B.S.**

Spread of cocaine use through both adolescent and adult communities has given rise to widespread concern and a considerable investment of

resources in an effort to contain that spread. Nonetheless, little is known of the way in which cocaine use has spread in the community and the extent to which factors involved in the spread of cocaine may differ for adults and adolescents. In addition, in spite of considerable effort to develop prevention programming, little is known about various factors which may influence cocaine use in vulnerable populations, or about the sources of information about the consequences of cocaine use which may be available to those populations and may be seen by them as being credible. Thus, this investigation examines issues which may impact the initiation of cocaine use by young people and their older peers. In addition, this study investigates sources of information about cocaine and the relative degree of credibility attached to these various sources.

The project involves samples of adolescents and adults in treatment for cocaine abuse. A structured interview schedule was used with subjects designed to determine: the histories of their drug-taking and, specifically, cocaine-using behaviors; the subjects' involvement in initiating others to cocaine use; and their experiences related to both cocaine use and other drug use in their peer groups. Using 10 centimeter analog scales, the study also explores ratings of availability and credibility of information sources about cocaine use and the significance attached to the several types of risks seen as consequent to cocaine use.

**C. Characteristics of Youth At Risk for Substance Abuse: Johnson, J., Brown, B.S., Hickey, J. and Jaffe, J.H.**

There is a need to identify risk factors associated with youth at risk for substance abuse and other dysfunctional behavior. Children have been viewed as being at particular risk for substance abuse when they come from homes in which parents have been engaged in substance abuse and/or antisocial activity.

In this study, samples consisting of 320 children and at least one biological parent are being selected as follows: children with alcoholic parents; children with parents who have abused substances other than alcohol; children of parents who have been engaged in antisocial behavior; and a control group of children who do not come from dysfunctional families. All children recruited are between the ages of 8 and 14 years. The children and at least one biological parent are administered a battery assessing current psychosocial functioning, family functioning, cognitive performance, and behaviors related to their interaction with the school and the community environments. To date, 71 children and their parents have been tested.

It is hoped that the results from this study will be important to efforts designed to structure prevention/early intervention programs targeted to the needs of specific populations. In

addition, the results of the study may clarify general risk factors shared by all groups relative to the formation of dysfunctional behavior.

## **Publications**

Bennett, L. and Johnson, J.: Adult Children of Alcoholics: Theory and Research. New Brunswick, NJ, Rutgers University, In press.

Brown, B.S. and Mills, A.: Youth at High Risk for Drug Abuse, A NIDA Research Monograph, Washington, DC, US Government Printing Office, 1987.

Brown, B.S., Rose, J.R., Weddington, W. and Jaffe, J.: Kids and cocaine: A treatment dilemma. J. Subst. Abuse Treat., In press.

Haertzen, C.A. and Hickey, J.E.: Addiction Research Center Inventory (ARCI): Measurement of Euphoria and Other Drug Effects. In Bozarth, M.A. (Ed.): Methods of Assessing the Reinforcing Properties of Abused Drugs. New York, NY, Springer-Verlag, 1987.

Herning, R.I., Hickey, J.E., Pickworth, W.B. and Jaffe, J.H.: Auditory event related potentials in adolescents at risk for drug abuse. Biol. Psychiat., In press.

Hickey, J.E., Kolar, A.F., Michaelson, B., Haynie, C., Chung, A. and Brosn, B.S.: The spread of cocaine use in adult and adolescent populations. Am. Acad. Child Adolescent Psychiat., In press.

Johnson, J.L., Rolf, J.E. and Rebeta, J.L.: Assessment of Brain Functioning in Individuals at Biosocial Risk: Examples from Alcoholic Families. In Petersen, A. (Ed.): Brain and Behavioral Development: Biosocial Perspectives, In press.

Johnson, J.L. and Bennett, L.: School-Aged Children of Alcoholics: Theory and Research, New Brunswick, NJ, Rutgers University, In press.

Johnson, J.L.: Issues in brain Imaging. Brit. J. Addict. 82: 1177-1179, 1987.

Johnson, J.L. and Rolf, J.E.: Cognitive performance patterns in children of alcoholics. Brit. J. Addict. 83: 849-857, 1988.

Rolf, J.E. and Johnson, J.L.: Protected or Vulnerable: AIDS Challenge to Developmental Psychopathology. In Rolf, J., Cicchetti, D., Neuchterlein, K., and Weintraub, S. (Eds.): Risk and Protective Factors in the Development of Psychopathology, In press.



## **Publications (Cont'd)**

Johnson, J.L., Rolf, J.E. and Israel, E.: Cognitive and academic performance in children of alcoholics. Brit. J. Addict., In press.

Rolf, J.E. and Johnson, J.L.: Depressive symptoms in children of alcoholics. Brit. J. Addict., In press.

## **Organizations Collaborating with the Treatment and Early Intervention Research Branch**

Maryland Substance Abuse Administration, Baltimore, MD

Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

Maryland Juvenile Services Administration, Baltimore, MD

Veterans Administration Hospital, Philadelphia, PA

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER ZO1 DA00001-02 TEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Physiological and Psychological Aspects of Cocaine Cessation		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;">           PI: E. Dax             Others: W.W. Weddington                      R.I. Herning                      E.J. Cone         </div> <div style="width: 30%;">           Chief             Visiting Scientist            Chief            Chief         </div> <div style="width: 30%;">           NEI, ARC, NIDA             CT, ARC, NIDA            CHP, ARC, NIDA            CIM, ARC, NIDA         </div> </div>		
COOPERATING UNITS (if any)  Chemistry and Drug Metabolism Laboratory, Cognitive Studies and Human Performance Laboratory, AIDS Laboratory		
LAB/BRANCH Clinical Trials Laboratory		
SECTION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
INSTITUTE AND LOCATION		
TOTAL MAN-YEARS: <div style="text-align: center;">0.65</div>	PROFESSIONAL: <div style="text-align: center;">0.25</div>	OTHER: <div style="text-align: center;">0.40</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <input checked="" type="checkbox"/> (a) Human subjects  <input type="checkbox"/> (a1) Minors  <input type="checkbox"/> (a2) Interviews         </div> <div style="width: 30%;"> <input type="checkbox"/> (b) Human tissues         </div> <div style="width: 30%;"> <input type="checkbox"/> (c) Neither         </div> </div>		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>This study examines behavioral and physiological aspects associated with the cessation of cocaine abuse by humans and provides longitudinal data regarding the psychological and physiological aspects of abstinence from cocaine. Specifically, an attempt will be made to examine craving for cocaine, changes in mood and cognition, cardiovascular function, sleep, and neuroendocrine functioning, as well as in the excretion of cocaine and its metabolites in urine and saliva, by persons who abruptly stop abusing cocaine after they are admitted to a research unit.</p> <p>Twelve cocaine addicts and six non-drug-abusing controls have been admitted and examined to date. Preliminary findings are that cocaine and its metabolites are measurable in saliva and urine for up to eight days following cessation of drug use. Also, cognitive functioning during the first four weeks of cocaine cessation is decreased compared to functioning at admission, with a trend toward improvement. Other preliminary findings in cocaine addicts initiating abstinence include persistent hyperprolactinemia and suppression of prolactin diurnal rhythm without alteration of cortisol rhythms. Craving for cocaine and reports of depression decrease markedly during the first two weeks after stopping cocaine use.</p>		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00002-02 TEI
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PERIOD COVERED  
October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Treatment for Cocaine Abuse: Trial of Amantadine and Desipramine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B.S. Brown	Chief	TEI, ARC, NIDA
Others:	W.W. Weddington	Visiting Scientist	CT, ARC, NIDA
	J.H. Jaffe	Director	ARC, NIDA

COOPERATING UNITS (if any)  
None

LAB/BRANCH  
Clinical Trials Laboratory

SECTION

INSTITUTE AND LOCATION  
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS: 2.90	PROFESSIONAL: 0.25	OTHER: 2.65
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CHECK APPROPRIATE BOX(ES)

<input checked="" type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purposes of this study were to longitudinally examine behavioral and physiological aspects regarding cessation of cocaine abuse by human subjects enrolled in an outpatient treatment program and to evaluate the efficacy of two drugs, amantadine and desipramine, in reducing craving for cocaine and increasing continuous abstinence from cocaine.

The study involves a single-blind, random-assignment, placebo-controlled, 12-week comparison of fixed doses of desipramine hydrochloride (200 mg/day) and amantadine hydrochloride (400 mg/day) as adjunctive treatments to counseling for cocaine dependence. Subjects were 54 outpatients who met Diagnostic and Statistical Manual, Third Edition (DSM-III-R) criteria for active cocaine dependence. Subjects treated with desipramine (N=17), amantadine (N=16), and placebo (N=21) did not differ with respect to cocaine use, route of drug administration, craving for cocaine, lifetime histories of psychopathology, admission scores on psychometric assessments, and sociodemographics. All treatment groups demonstrated dramatic and persistent decreases in cocaine use, craving for cocaine, and psychiatric symptoms compared to intake values.



**Treatment for Cocaine Abuse: Trial of Amantadine and Desipramine**

There were no significant differences between treatment groups for retention in treatment, craving for cocaine, or cocaine use during treatment, although subjects treated with desipramine were somewhat more likely ( $p < 0.10$ ) to have longer periods of abstinence from cocaine than the subjects in other groups.

**Publications and Presentations**

Weddington, W.W. and Brown, B.S.: Acceptance of HIV-antibody testing by persons seeking outpatient treatment for cocaine abuse. J. Subst. Abuse Treat. 5: 145-149, 1988.

Weddington, W.W. and Brown, B.S.: Acceptance of HIV-antibody testing by cocaine-abusing outpatients. Poster Session, Annual Meeting of the American Psychiatric Association, Montreal, Canada, May 10, 1988.

Weddington, W.W. and Brown, B.S.: HIV-antibody testing of patients seeking treatment for drug abuse. Workshop, 40th Institute on Hospital and Community Psychiatry, New Orleans, LA, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 DA00003-02 TEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Characteristics of Waiting List Clients and Behaviors		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	B.S. Brown	Chief TEI, ARC, NIDA
Others:	J.E. Hickey J.H. Jaffe	Social Worker Director TEI, ARC, NIDA ARC, NIDA
COOPERATING UNITS (if any) Maryland Substance Abuse Administration (X-Cell Program)		
LAB/BRANCH Clinical Trials Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.50	PROFESSIONAL: 0.25	OTHER: 0.25
CHECK APPROPRIATE BOX(ES) . <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>Programs in many parts of the country are reporting lengthy waiting lists for entry into drug abuse treatment. The effect on people's behavior and thinking relative to being on a waiting list is unknown. This study explored the waiting list behaviors of persons who registered for treatment at one area cocaine abuse treatment program. A random sample of 29 applicants for treatment was interviewed using a structured interview schedule exploring drug and alcohol use, antisocial and prosocial behaviors, relations with friends and family, efforts to locate other treatment resources, satisfaction with self, and future expectations. These behaviors were assessed for the period that subjects were on the waiting list. In addition, exploration was made of both psychological symptoms and AIDS-related risk-taking/risk-reducing behaviors.</p> <p>Nearly half the applicants (48.3%) reported having significantly reduced drug use in association with their applying for treatment, but most applicants (58.6%) were pessimistic about their long-term capacity to remain free of drug-related difficulty.</p>		

### Characteristics of Waiting List Clients and Behaviors

As a group, subjects' Symptom Checklist-90-Revised (SCL-90-R) scores were consistent with an interpretation of major depression; nonetheless, a majority of applicants (51.7%) reported themselves as having become less interested in entering treatment. Nearly all applicants reported high levels of encouragement for their decision to enter treatment from persons with whom they were living and about half reported encouragement from their friends.

Of the 23 applicants who were IV drug users, 10 (41.7%) reported knowing someone who had contracted AIDS, 87.0% reported having changed behaviors, chiefly needle sharing, to reduce the risk of infection, and 69.6% reported having obtained HIV testing.

The results of this study would seem to call into question the capacity of a waiting list to act as support to drug abuse treatment.

### Publications

Brown, B.S., Hickey, J.E., Chung, A.S., Craig, R.D. and Jaffe, J.H.: The functioning of individuals on a drug abuse treatment waiting list. Am. J. Drug Alcohol Abuse, In press.

Brown, B.S., Hickey, J.E., Chung, A.S., Craig, R.D. and Jaffe, J.H.: Waiting for treatment: Behaviors of cocaine users on a waiting list. Committee on Problems of Drug Dependence, In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER <b>Z01 DA00004-02 TEI</b>
PERIOD COVERED <b>October 1, 1987 to December 31, 1988</b>		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Cocaine Abuse Treatment for Clients Receiving Methadone Maintenance</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: <b>A.F. Kolar</b>	<b>Staff Fellow</b>	<b>CT, ARC, NIDA</b>
Others: <b>B.S. Brown</b> <b>J.H. Jaffe</b>	<b>Chief</b> <b>Director</b>	<b>TEI, ARC, NIDA</b> <b>ARC, NIDA</b>
COOPERATING UNITS (if any)  <b>Maryland Substance Abuse Administration (Man Alive Program)</b>		
LAB/BRANCH <b>Clinical Trials Laboratory</b>		
SECTION		
INSTITUTE AND LOCATION <b>Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD   21224</b>		
TOTAL MAN-YEARS: <b>2.90</b>	PROFESSIONAL: <b>0.40</b>	OTHER: <b>2.50</b>
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)  <p>             Methadone programs are reporting significant numbers of clients remaining opiate-free while becoming involved in continuing patterns of cocaine abuse. The purpose of this study is to assess the efficacy of pharmacologic adjuncts to methadone maintenance treatment in regimens that have been suggested as being useful in earlier work with cocaine abuse clients. In a double-blind study, methadone maintenance clients, who exhibit consistently urine toxicologies positive for cocaine, are randomly assigned to one of three medication groups: desipramine hydrochloride, amantadine hydrochloride, and placebo. A total of 15 subjects in each cell is anticipated. The intervention lasts a total of 12 weeks. Measures are taken of drug use, client mood, psychological symptoms, depressive functioning, drug craving, sleep satisfaction, and reported drug effects using a repeated-measures design. In addition, there will be followup of clients at 6 and 12 months post-treatment. Study findings may be expected to have significance for efforts to successfully treat opiate clients and thereby may have importance for efforts to contain the spread of HIV infection as well. Twenty-four subjects have been recruited to date.           </p>		

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00005-02 TEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Spread of Cocaine in Adult and Adolescent Populations		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.E. Hickey	Social Worker TEI, ARC, NIDA
Others:	B.S. Brown	Chief TEI, ARC, NIDA
COOPERATING UNITS (if any) Maryland Substance Abuse Administration (Epoch Counseling Centers, X-Cell Program)		
LAB/BRANCH Early Intervention Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 0.50	PROFESSIONAL: 0.25	OTHER: 0.25
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input checked="" type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided )  <p>The purpose of this study was to examine similarities and differences between samples of adult and youthful cocaine users in terms of the process of initiation into cocaine use, the course of involvement with cocaine, the initiation of others in cocaine use, the threats seen as posed by cocaine use to self, friendship and family relationships and the supports offered for and against cocaine use, as well as sources of information about cocaine seen as available to the subject and the credibility attached to those various information sources. A sample of 90 adults (26 years and older) and 20 youths (21 years and below), stratified by gender and ethnicity, was drawn from area residential and outpatient programs. Structured close-ended interview schedules were administered to assess issues involving cocaine use as described above. In addition, information was obtained regarding relevant background and demographic characteristics. Data have been gathered on 110 subjects.</p> <p>Study findings clarifying issues in the initiation of cocaine use, its spread to others, and the availability and credibility of information sources about cocaine may be useful to the development of early intervention and prevention efforts.</p>		

Z01 DA0005-02 TEI (Cont'd)

**Spread of Cocaine in Adult and Adolescent Populations**

**Publications**

Hickey, J.E., Kolar, A.F., Michaelson, B., Haynie, C., Chung, A. and Brown, B.S.: The spread of cocaine use in adult and adolescent populations. Amer. Acad. Child Adolescent Psychiat., In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00006-02 TEI
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PERIOD COVERED October 1, 1987 to December 31, 1988
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TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Family Intervention with Young Chronic Cocaine Abusers
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PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)			
PI:	J. Rose	Social Worker	TEI, ARC, NIDA
Others:	B.S. Brown	Chief	TEI, ARC, NIDA
	J.H. Jaffe	Director	ARC, NIDA
	W.W. Weddington	Visiting Scientist	CT, ARC, NIDA

COOPERATING UNITS (if any)  Maryland Juvenile Services Administration
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LAB/BRANCH Early Intervention Laboratory
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SECTION
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INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224
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TOTAL MAN-YEARS: 1.00	PROFESSIONAL: 0.25	OTHER: 0.75
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CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) Human subjects	<input type="checkbox"/> (b) Human tissues	<input type="checkbox"/> (c) Neither
<input checked="" type="checkbox"/> (a1) Minors		
<input checked="" type="checkbox"/> (a2) Interviews		

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
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The purpose of this study was to examine the efficacy of traditional family therapy with a family therapy regimen making use of urine toxicology reports, such that parents can monitor their adolescents' drug use. Twelve adolescents and their families were randomly assigned to one of two treatment conditions: family therapy with toxicology reports and family therapy only. Treatment lasted 24 weeks with twice weekly sessions (one family and one individual) in which trained counselors followed a standard regimen. Measures of substance abuse, psychological functioning, and family functioning were obtained pre- and post-treatment.

The major and unexpected finding from this study was the difficulty experienced in recruiting subjects. Despite aggressive efforts and the availability of free treatment, the study obtained only 12 cocaine-using (21 years and younger) youngsters over a period of 9 months, compared to 122 adult cocaine users.

### Family Intervention with Young Chronic Cocaine Abusers

An examination of admissions data for Baltimore and other jurisdictions indicated this experience was typical. However, household survey data indicate that, based on the frequency of cocaine use, a much greater proportion of treatment admissions might be expected to be derived from persons 21 years and younger. These findings speak to the particular importance of early intervention strategies with this population.

### Publications

Brown, B.S., Rose, M.R., Weddington, W.W. and Jaffe, J.H.: Kids and cocaine - A treatment dilemma. J. Subst. Abuse Treat., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 DA00007-02 TEI																								
PERIOD COVERED April 1987 to June 1988																										
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Opioid Dependence Intervention: Pharmacologic Study of Buprenorphine</b>																										
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">PI: R.E. Johnson</td> <td style="width: 30%;">Chief</td> <td style="width: 40%;">RS, ARC, NIDA</td> </tr> <tr> <td>Others: P.J. Fudala</td> <td>Staff Fellow</td> <td>ARC, NIDA</td> </tr> <tr> <td>E.J. Cone</td> <td>Chief</td> <td>CDM, ARC, NIDA</td> </tr> <tr> <td>E.M. Dax</td> <td>Chief</td> <td>NEI, ARC, NIDA</td> </tr> <tr> <td>J.E. Henningfield</td> <td>Chief</td> <td>BDL, ARC, NIDA</td> </tr> <tr> <td>R.I. Herning</td> <td>Chief</td> <td>CHP, ARC, NIDA</td> </tr> <tr> <td>W.R. Lange</td> <td>Medical Director</td> <td>NEI, ARC, NIDA</td> </tr> <tr> <td>W.W. Weddington</td> <td>Visiting Scientist</td> <td>CT, ARC, NIDA</td> </tr> </table>			PI: R.E. Johnson	Chief	RS, ARC, NIDA	Others: P.J. Fudala	Staff Fellow	ARC, NIDA	E.J. Cone	Chief	CDM, ARC, NIDA	E.M. Dax	Chief	NEI, ARC, NIDA	J.E. Henningfield	Chief	BDL, ARC, NIDA	R.I. Herning	Chief	CHP, ARC, NIDA	W.R. Lange	Medical Director	NEI, ARC, NIDA	W.W. Weddington	Visiting Scientist	CT, ARC, NIDA
PI: R.E. Johnson	Chief	RS, ARC, NIDA																								
Others: P.J. Fudala	Staff Fellow	ARC, NIDA																								
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R.I. Herning	Chief	CHP, ARC, NIDA																								
W.R. Lange	Medical Director	NEI, ARC, NIDA																								
W.W. Weddington	Visiting Scientist	CT, ARC, NIDA																								
COOPERATING UNITS (if any) Research Support Branch, Chemistry & Drug Metabolism, Neuroendocrine/Immunology, Biology of Dependence & Abuse Potential Assessment, Cognitive Studies and Human Performance, Clinical Trials,																										
LAB/BRANCH Treatment and Early Intervention Laboratory																										
SECTION																										
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224																										
TOTAL MAN-YEARS: <div style="text-align: center;">5.40</div>	PROFESSIONAL: <div style="text-align: center;">1.90</div>	OTHER: <div style="text-align: center;">3.50</div>																								
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews																										
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>A rapid dose-induction procedure used in nineteen male, heroin-dependent, volunteer subjects who were given buprenorphine (BUP) in ascending daily sublingual dosages of 2, 4 and 8 mg demonstrated that heroin-dependent individuals can be rapidly inducted onto BUP without precipitating withdrawal, while being provided maximum mu-agonist effects.</p> <p>Using a parallel-group design, eighteen of these subjects were randomly assigned to one of two groups (A or B; 9 per group). On days 19 through 30, Group A continued on an every-day dosing schedule, while Group B received BUP every other day; then, both groups were abruptly withdrawn from BUP. The results indicate that BUP can be administered on an every-other-day schedule with only minimal symptoms of withdrawal; however, BUP's ability to block the mu-agonist properties of IV hydromorphone 30 hours after the last dose of BUP was minimal with clinically significant effects being observed for subject-rated "drug-liking," MBG (euphoria) scale scores, and pupillary constriction.</p>																										



**Opioid Dependence Intervention: A Pharmacologic Study of Buprenorphine**

When BUP was abruptly terminated, peak withdrawal occurred between 72 and 168 hours following the last dose of BUP, with the response for Group A tending to be higher than for Group B. Peak responses in Group B occurred earlier than Group A for subject-rated "level of withdrawal," "overall discomfort," and "need for opiate," but not for "overall sickness."

Notably, results on a 15-item withdrawal adjective checklist did not demonstrate statistically significant differences between the two groups, with peak scores occurring 120 hours following the last BUP dose.

The changes in response which were observed generally returned to baseline by 10 days. Subject-rated duration of sleep was lowest in Group A. By the 13th day following the last dose of BUP, self-reported sleep had returned to baseline levels for Group B, but not Group A.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00008-01 TEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Characteristics of Youths at Differential Risk for Substance Abuse		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J. Johnson	Psychologist ARC, NIDA
Others:	B.S. Brown	Chief TEI, ARC, NIDA
	J.H. Jaffe	Director ARC, NIDA
	J. Hickey	Social Worker TEI, ARC, NIDA
COOPERATING UNITS (if any) Psychology of Vulnerability Laboratory		
LAB/BRANCH Treatment and Early Intervention Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS: 1.50	PROFESSIONAL: 1.50	OTHER: 0.00
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input checked="" type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>             This study will contrast the different types of family experiences that children have coming from different substance-abusing families in order to identify risk factors that lead some children to abuse substances, yet apparently do not influence others. Children have been seen as being at particular risk for substance abuse when coming from homes in which significant dysfunctional behavior has been evident. Children seen at risk include: (1) children of alcoholic parents, (2) children of parents who have abused substances other than alcohol, and (3) children whose parents have engaged in antisocial behaviors. These three groups would be compared with a group of control children who do not come from dysfunctional families. A total of 320 children and at least one of their biological parents will be sampled for this study. All parents and children will be volunteers. Children will be between the ages of 8 and 14 years, will consist of equal numbers of males and females, and will represent the three groups described above as well as an additional 80 youngsters whose parents have no involvement with either substance abuse or antisocial behavior.           </p>		

**Characteristics of Youths at Differential Risk for Substance Abuse**

It is hoped that this research activity will advance the present base of knowledge as it relates to possible prevention and intervention projects which may be directed toward reducing drug abuse. This basic research study is important to the development of future studies which may be designed to evaluate the potential efficacy various approaches may have to prevent drug use or abuse.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DA00009-01 TEI
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## PERIOD COVERED

October 1, 1987 to December 31, 1988

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Efficacy of Fluoxetine in the Treatment of Cocaine and Phencyclidine Dependence

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B.S. Brown	Chief	TEI, ARC, NIDA
Others:	L. Covi	Visiting Scientist	ARC, NIDA
	J.H. Jaffe	Director	ARC, NIDA

## COOPERATING UNITS (if any)

Psychology of Vulnerability Laboratory

## LAB/BRANCH

Treatment and Early Intervention Laboratory

## SECTION

## INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

## TOTAL MAN-YEARS:

4.20

## PROFESSIONAL:

0.50

## OTHER:

3.70

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects
☐ (b) Human tissues
☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This study assesses the efficacy of different pharmacologic adjuncts in the treatment of cocaine and phencyclidine (PCP) dependence. Initial work over the course of the past year focused on fluoxetine, contrasting the efficacy of this serotonergic reuptake blocker with a placebo condition. A double-blind, random assignment, placebo-control, 12-week study was designed to compare three dosage levels of fluoxetine (20 mg, 40 mg and 60 mg) with a placebo (i.e., diphenhydramine) condition using the pharmacologic adjunct in addition to counseling for cocaine and PCP users. Subjects must meet DSM-III-R criteria for active dependence. To date, a total of 46 cocaine-dependent subjects and 14 PCP-dependent subjects have been involved in the study. Weekly ratings are obtained for cocaine and PCP use, craving, depression, sleep patterns, and mood disturbance. In addition, pre- and post-study measures are taken for psychiatric symptom scores and community functioning. Three-, 6- and 12-month followup assessments are also planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER Z01 DA00017-01 TEI
PERIOD COVERED October 1, 1987 to December 31, 1988		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) The Effectiveness of Methadone Maintenance Treatment		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	B.S. Brown	Chief TEI, ARC, NIDA
Others:	J.C. Ball	Visiting Scientist ARC, NIDA
COOPERATING UNITS (if any) John F. Kennedy Community Center, Glenwood Life Counseling Center, Achievement through Counseling & Treatment, Bridge Plaza Treatment & Rehabilitation Center, Man Alive, Inc., Fort Greene Treatment Center, Philadelphia VA Hospital		
LAB/BRANCH Treatment and Early Intervention Laboratory		
SECTION		
INSTITUTE AND LOCATION Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.00	1.00	1.00
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Methadone maintenance treatment is effective in reducing the risk of AIDS; that is, 71% of patients cease IV drug use during treatment ( <u>J. Health Soc. Behav.</u> , In press). However, some programs are markedly more effective than others; success ranges from over 90% who stop IV use to less than 50%. Thus, a significant goal is to determine characteristics of the more successful methadone maintenance programs.  In pursuit of this aim, data pertaining to 99 program variables were collected on-site from seven methadone programs in New York, Philadelphia, and Baltimore. Analysis of these findings showed that more successful programs were characterized by: a long-term methadone maintenance policy, an experienced full-time director, coordinated management of treatment services, adequate counseling staff, experienced and dedicated counselors, the availability of group counseling and some ex-addict staff, adequate medical coverage (i.e., higher percent of patients routinely treated), and high staff morale.		

**The Effectiveness of Methadone Maintenance Treatment**

Measurement and analysis of these program variables reveal that there are two types of successful programs: those which focus upon social rehabilitation and those which emphasize medical-psychiatric treatment

**Publications and Presentations**

Ball, J.C. and Corty, E.: Policy Issues Pertaining to the Treatment of Heroin Addictions in the United States - With Particular Reference to Methadone Maintenance Therapy. Proceedings of the Dutch-American Conference: The Effectiveness of Drug Abuse Treatment, In press.

Ball, J.C., Large, W.R., Myers, C.P. and Friedman, S.: Reducing the risk of AIDS through methadone maintenance treatment. J. Health Soc. Behav., In press.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00018-01 TEI

PERIOD COVERED

October 1, 1987 to December 31, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Buprenorphine/Methadone Comparison - Maintenance and Detoxification

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.E. Johnson	Chief	RS, ARC, NIDA
Others:	P.J. Fudala	Staff Fellow	ARC, NIDA
	W.R. Lange	Medical Director	NET, ARC, NIDA
	J.C. Ball	Visiting Scientist	ARC, NIDA
	B.S. Brown	Chief	TEI, ARC, NIDA
	J.H. Jaffe	Director	ARC, NIDA

COOPERATING UNITS (if any)

Research Support Branch, Clinical Trials Laboratory, Psychology of Vulnerability Laboratory

LAB/BRANCH

Early Intervention and Treatment Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:

11.20

PROFESSIONAL:

2.80

OTHER:

8.40

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Previous studies in this Laboratory assessing buprenorphine's pharmacodynamic and pharmacokinetic properties in opioid abusers and opioid-dependent individuals have provided evidence that buprenorphine has potential utility in treating opioid dependence. Since it has been reported that many IV drug abusers refuse to enter treatment due to their feeling that methadone would make their addiction worse (Rounsaville and Kleber, 1985) and, given the association between AIDS and IV drug users, buprenorphine could have a positive impact on public health if its therapeutic utility can be demonstrated in a well-designed and controlled non-residential setting.

In this study, up to 150 opioid-dependent individuals will be enrolled into an 180-day detoxification protocol. Subjects will be randomly assigned to different treatment groups. Each group will receive methadone or buprenorphine. Doses will be given under double-blind, double-dummy (i.e., methadone orally or buprenorphine sublingually) conditions.

**Buprenorphine/Methadone Comparison - Maintenance and Detoxification**

Subjects will receive routine non-medical treatment services in accord with their needs and functioning as well as individual counseling once weekly. All clinic staff will be blind regarding the subjects' treatment group to eliminate potential bias.

The purpose of this study is to determine the effectiveness of buprenorphine in maintaining opioid-dependent individuals in outpatient treatment as compared to the prototypic maintenance drug, methadone. Dependent variables will include: (1) retention time in study; (2) missed clinic visits; (3) indicators of illicit drug use (i.e., urines positive for illicit drugs) and blood alcohol levels greater than 0.05 gm%; (4) subject-reported side effects and depression; (5) subject-reported opiate-like or opiate-related withdrawal effects; and, (6) blood chemistries and urinalysis to measure potential drug toxicity. This study is designed to provide pivotal data for submission to the Food and Drug Administration in support of a new indication for buprenorphine.

















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